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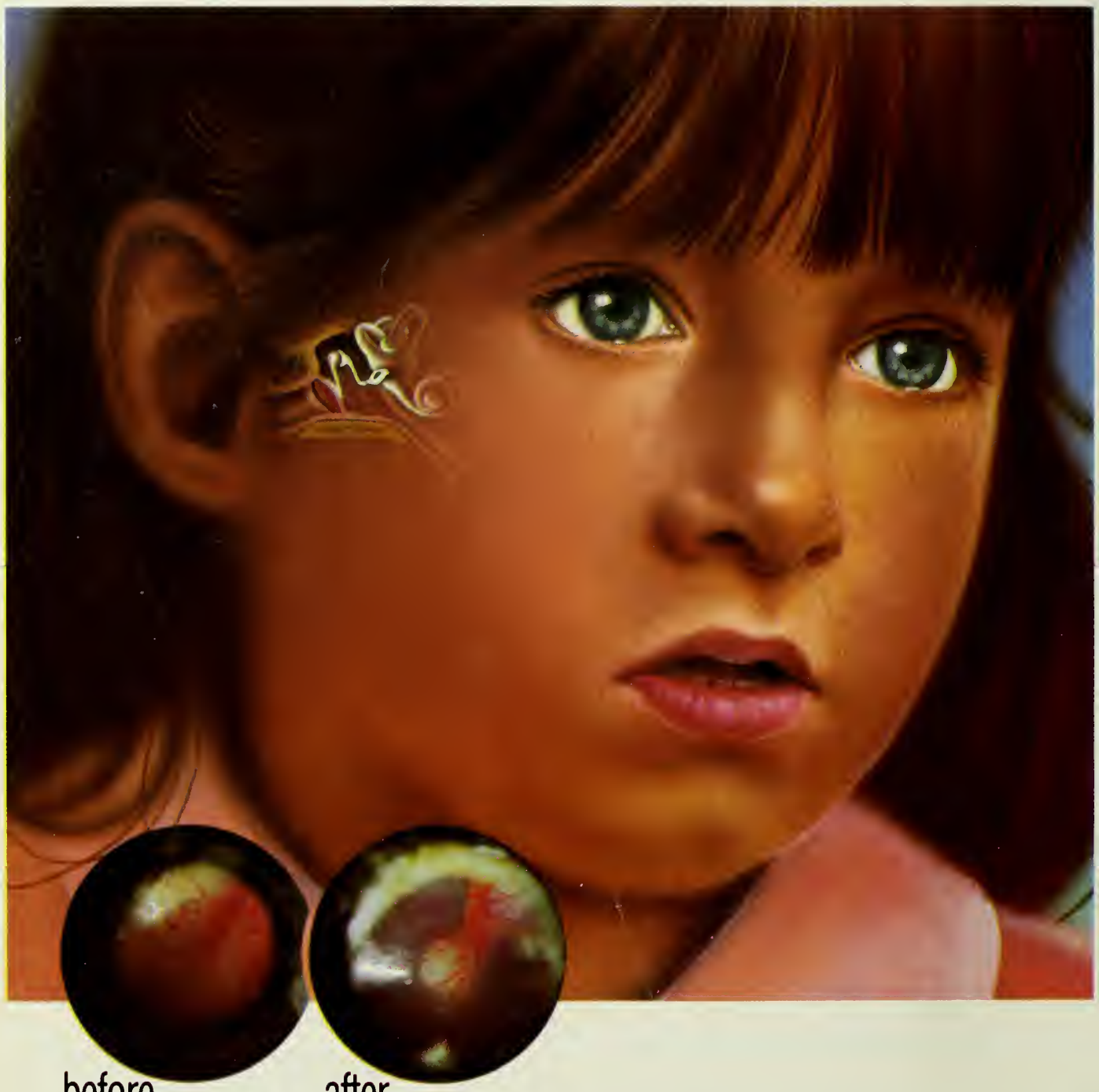

before Otoscopic view of tympanic membrane in a patient who did not respond to ampicillin

after Same patient after ten days of Bactrim (trimethoprim and sulfamethoxazole/Roche) therapy

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Overall, 86% of *Haemophilus influenzae* strains taken from sputum cultures prove susceptible *in vitro* to Bactrim.[4] In one study, 100% of 191 ampicillin-resistant *H. influenzae* isolates were susceptible to Bactrim.[5] However, *in vitro* data do not necessarily correlate with clinical results.

Active against 91% of *S. pneumoniae in vitro*

In sputum cultures of *Streptococcus pneumoniae*, the most frequent pathogen in acute otitis media, 91% of isolates show susceptibility *in vitro* to Bactrim.[4]

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And the average cost of Bactrim is lower than that of cefaclor and comparable to that of ampicillin and amoxicillin.[7]
Bactrim is indicated in acute otitis media due to susceptible organisms when it offers an advantage over other antimicrobials. Bactrim is contraindicated in pregnancy, lactation, infants under two months of age and documented megaloblastic anemia due to folate deficiency. To date, there are limited data on the safety of repeated use of Bactrim in children under two years of age.

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Please see references and summary of product information on following page.

References: 1. Klimek JJ *et al: J Pediatr* 96:1087-1089, Jun 1980. 2. Schwartz RH *et al: Rev Infect Di* 4:514-516, Mar-Apr 1982. 3. Cooper J, Inman JS, Dawson AF: *Practitioner* 217:804-809, Nov 1976. 4. Antibiotic Sensitivity Report, Winter 1983. BAC-DATA Medical Information Systems, Inc. 5. Data on file, Hoffmann-La Roche Inc., Nutley, NJ. 6. Wormser GP, Keusch GT, Heel RC: *Drugs* 24:459-518, Dec 1982. 7. *Med Lett Drugs Ther* 23:93-95, Oct 30, 1981.

BACTRIM™ (trimethoprim and sulfamethoxazole/Roche)

Before prescribing, please consult complete product information, a summary of which follows:

Indications and Usage: For the treatment of urinary tract infections due to susceptible strains of the following organisms: *Escherichia coli, Klebsiella-Enterobacter, Proteus mirabilis, Proteus vulgaris, Proteus morganii.* It is recommended that initial episodes of uncomplicated urinary tract infections be treated with a single effective antibacterial agent rather than the combination. *Note:* The increasing frequency of resistant organisms limits the usefulness of all antibacterials, especially in these urinary tract infections.

For acute otitis media in children due to susceptible strains of *Haemophilus influenzae* or *Streptococcus pneumoniae* when in physician's judgment it offers an advantage over other antimicrobials. To date, there are limited data on the safety of repeated use of Bactrim in children under two years of age. Bactrim is not indicated for prophylactic or prolonged administration in otitis media at any age.

For acute exacerbations of chronic bronchitis in adults due to susceptible strains of *Haemophilus influenzae* or *Streptococcus pneumoniae* when in physician's judgment it offers an advantage over a single antimicrobial agent.

For enteritis due to susceptible strains of *Shigella flexneri* and *Shigella sonnei* when antibacterial therapy is indicated.

Also for the treatment of documented *Pneumocystis carinii* pneumonitis.

Contraindications: Hypersensitivity to trimethoprim or sulfonamides; patients with documented megaloblastic anemia due to folate deficiency; pregnancy at term; nursing mothers because sulfonamides are excreted in human milk and may cause kernicterus; infants less than 2 months of age.

Warnings: BACTRIM SHOULD NOT BE USED TO TREAT STREPTOCOCCAL PHARYNGITIS. Clinical studies show that patients with group A β-hemolytic streptococcal tonsillopharyngitis have higher incidence of bacteriologic failure when treated with Bactrim than do those treated with penicillin. Deaths from hypersensitivity reactions, hepatocellular necrosis, agranulocytosis, aplastic anemia and other blood dyscrasias have been associated with sulfonamides. Experience with trimethoprim is much more limited but occasional interference with hematopoiesis has been reported as well as an increased incidence of thrombopenia with purpura in elderly patients on certain diuretics, primarily thiazides. Sore throat, fever, pallor, purpura or jaundice may be early signs of serious blood disorders. Frequent CBC's are recommended; therapy should be discontinued if a significantly reduced count of any formed blood element is noted.

Precautions: *General:* Use cautiously in patients with impaired renal or hepatic function, possible folate deficiency, severe allergy or bronchial asthma. In patients with glucose-6-phosphate dehydrogenase deficiency, hemolysis, frequently dose-related, may occur. During therapy, maintain adequate fluid intake and perform frequent urinalyses, with careful microscopic examination, and renal function tests, particularly where there is impaired renal function. Bactrim may prolong prothrombin time in those receiving warfarin; reassess coagulation time when administering Bactrim to these patients.

Pregnancy: Teratogenic Effects: Pregnancy Category C. Because trimethoprim and sulfamethoxazole may interfere with folic acid metabolism, use during pregnancy only if potential benefits justify the potential risk to the fetus.

Adverse Reactions: All major reactions to sulfonamides and trimethoprim are included, even if not reported with Bactrim. *Blood dyscrasias:* Agranulocytosis, aplastic anemia, megaloblastic anemia, thrombopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia and methemoglobinemia. *Allergic reactions:* Erythema multiforme, Stevens-Johnson syndrome, generalized skin eruptions, epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia and allergic myocarditis. *Gastrointestinal reactions:* Glossitis, stomatitis, nausea, emesis, abdominal pains, hepatitis, hepatocellular necrosis, diarrhea, pseudomembranous colitis and pancreatitis. *CNS reactions:* Headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo, insomnia, apathy, fatigue, muscle weakness and nervousness. *Miscellaneous reactions:* Drug fever, chills, toxic nephrosis with oliguria and anuria, periarteritis nodosa and L.E. phenomenon. Due to certain chemical similarities to some goitrogens, diuretics (acetazolamide, thiazides) and oral hypoglycemic agents, sulfonamides have caused rare instances of goiter production, diuresis and hypoglycemia in patients; cross-sensitivity with these agents may exist. In rats, long-term therapy with sulfonamides has produced thyroid malignancies.

Dosage: Not recommended for infants less than two months of age.

URINARY TRACT INFECTIONS AND SHIGELLOSIS IN ADULTS AND CHILDREN, AND ACUTE OTITIS MEDIA IN CHILDREN:

Adults: Usual adult dosage for urinary tract infections—1 DS tablet (double strength), 2 tablets (single strength) or 4 teasp. (20 ml) b.i.d. for 10-14 days. Use identical daily dosage for 5 days for shigellosis.

Children: Recommended dosage for children with urinary tract infections or acute otitis media—8 mg/kg trimethoprim and 40 mg/kg sulfamethoxazole per 24 hours, in two divided doses for 10 days. Use identical daily dosage for 5 days for shigellosis.

For patients with renal impairment: Use recommended dosage regimen when creatinine clearance is above 30 ml/min. If creatinine clearance is between 15 and 30 ml/min, use one-half the usual regimen. Bactrim is not recommended if creatinine clearance is below 15 ml/min.

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Usual adult dosage: 1 DS tablet (double strength), 2 tablets (single strength) or 4 teasp. (20 ml) b.i.d. for 14 days.

PNEUMOCYSTIS CARINII PNEUMONITIS:

Recommended dosage: 20 mg/kg trimethoprim and 100 mg/kg sulfamethoxazole per 24 hours in equal doses every 6 hours for 14 days. See complete product information for suggested children's dosage table.

Supplied: *Double Strength (DS) tablets*, each containing 160 mg trimethoprim and 800 mg sulfamethoxazole, bottles of 100, 250 and 500; Tel-E-Dose® packages of 100; Prescription Paks of 20. *Tablets*, each containing 80 mg trimethoprim and 400 mg sulfamethoxazole—bottles of 100 and 500; Tel-E-Dose® packages of 100; Prescription Paks of 40. *Pediatric Suspension*, containing 40 mg trimethoprim and 200 mg sulfamethoxazole per teaspoonful (5 ml); cherry flavored—bottles of 100 ml and 16 oz (1 pint). *Suspension*, containing 40 mg trimethoprim and 200 mg sulfamethoxazole per teaspoonful (5 ml); fruit-licorice flavored—bottles of 16 oz (1 pint).

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INDICATIONS AND USAGE: SORBITRATE (isosorbide dinitrate) is indicated for the treatment and prevention of angina pectoris. All dosage forms of isosorbide dinitrate may be used prophylactically to decrease frequency and severity of anginal attacks and can be expected to decrease the need for sublingual nitroglycerin.

The sublingual and chewable forms of the drug are indicated for acute prophylaxis of angina pectoris when taken a few minutes before situations likely to provoke anginal attacks. Because of a slower onset of effect, the oral forms of isosorbide dinitrate are not indicated for acute prophylaxis.

CONTRAINDICATIONS: SORBITRATE is contraindicated in patients who have shown purported hypersensitivity or idiosyncrasy to it or other nitrates or nitrites. Epinephrine and related compounds are ineffective in reversing the severe hypotensive events associated with overdose and are contraindicated in this situation.

WARNINGS: The benefits of SORBITRATE during the early days of an acute myocardial infarction have not been established. If one elects to use organic nitrates in early infarction, hemodynamic monitoring and frequent clinical assessment should be used because of the potential deleterious effects of hypotension.

PRECAUTIONS: General: Severe hypotensive response, particularly with upright posture, may occur with even small doses of SORBITRATE. The drug should therefore be used with caution in subjects who may have blood volume depletion from diuretic therapy or in subjects who have low systolic blood pressure (eg, below 90 mmHg). Paradoxical bradycardia and increased angina pectoris may accompany nitrate-induced hypotension. Nitrate therapy may aggravate the angina caused by hypertrophic cardiomyopathy.

Marked symptomatic, orthostatic hypotension has been reported when calcium channel blockers and organic nitrates were used in combination. Dose adjustment of either class of agents may be necessary.

Tolerance to this drug and cross-tolerance to other nitrates and nitrites may occur. Tolerance to the vascular and antianginal effects of isosorbide dinitrate or nitroglycerin has been demonstrated in clinical trials, experience through occupational exposure, and in isolated tissue experiments in the laboratory. The importance of tolerance to the appropriate use of isosorbide dinitrate in the management of patients with angina pectoris has not been determined. However, one clinical trial using treadmill exercise tolerance (as an end point) found an 8-hour duration of action of oral isosorbide dinitrate following the first dose (after a 2-week placebo washout) and only a 2-hour duration of effect of the same dose after 1 week of repetitive dosing at conventional dosing intervals. On the other hand, several trials have been able to differentiate isosorbide dinitrate from placebo after 4 weeks of therapy and, in open trials, an effect seems detectable for as long as several months.

Tolerance clearly occurs in industrial workers continuously exposed to nitroglycerin. Moreover, physical dependence also occurs since chest pain, acute myocardial infarction, and even sudden death have occurred during temporary withdrawal of nitroglycerin from the workers. In clinical trials in angina patients, there are reports of anginal attacks being more easily provoked and of rebound in the hemodynamic effects soon after nitrate withdrawal. The relative importance of these observations to the routine, clinical use of isosorbide dinitrate is not known. However, it seems prudent to gradually withdraw patients from isosorbide dinitrate when the therapy is being terminated, rather than stopping the drug abruptly.

Information for Patients: Headache may occur during initial therapy with SORBITRATE. Headache is usually relieved by the use of standard headache remedies or by lowering the dose and tends to disappear after the first week or two of use.

Drug Interactions: Alcohol may enhance any marked sensitivity to the hypotensive effect of nitrates.

Isosorbide dinitrate acts directly on vascular smooth muscle, therefore, any other agent that depends on vascular smooth muscle as the final common path can be expected to have decreased or increased effect depending on the agent.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No long-term studies in animals have been performed to evaluate the carcinogenic potential of this drug. A modified two-litter reproduction study in rats fed isosorbide dinitrate at 25 or 100 mg/kg/day did not reveal any effects on fertility or gestation or any remarkable gross pathology in any parent or offspring fed isosorbide dinitrate as compared with rats fed a basal-controlled diet.

Pregnancy Category C: Isosorbide dinitrate has been shown to cause a dose-related increase in embryotoxicity (increase in mummified pups) in rabbits at oral doses 35 and 150 times the maximum recommended human daily dose. There are no adequate and well-controlled studies in pregnant women. SORBITRATE should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when SORBITRATE is administered to a nursing woman.

Pediatric Use: The safety and effectiveness of SORBITRATE in children has not been established.

ADVERSE REACTIONS: Adverse reactions, particularly headache and hypotension, are dose-related. In clinical trials at various doses, the following have been observed.

Headache is the most common (reported incidence varies widely, apparently being dose-related, with an average occurrence of about 25%) adverse reaction and may be severe and persistent. Cutaneous vasodilation with flushing may occur. Transient episodes of dizziness and weakness, as well as other signs of cerebral ischemia associated with postural hypotension, may occasionally develop (the incidence of reported symptomatic hypotension ranges from 2% to 36%). An occasional individual will exhibit marked sensitivity to the hypotensive effects of nitrates and severe responses (nausea, vomiting, weakness, restlessness, pallor, perspiration, and collapse) may occur even with the usual therapeutic dose. Drug rash and/or exfoliative dermatitis may occasionally occur. Nausea and vomiting appear to be uncommon. Case reports of clinically significant methemoglobinemia are rare at conventional doses of organic nitrates. The formation of methemoglobin is dose-related and, in the case of genetic abnormalities of hemoglobin that favor methemoglobin formation, even conventional doses of organic nitrate could produce harmful concentrations of methemoglobin.

DOSAGE AND ADMINISTRATION: For the treatment of angina pectoris, the usual starting dose for sublingual SORBITRATE is 2.5 to 5 mg; for chewable tablets, 5 mg, for oral (swallowed) tablets, 5 to 20 mg, and for controlled-release forms, 40 mg.

SORBITRATE should be titrated upward until angina is relieved or side effects limit the dose. In ambulatory patients, the magnitude of the incremental dose increase should be guided by measurements of standing blood pressure.

The initial dosage of sublingual or chewable SORBITRATE for prophylactic therapy in angina pectoris patients is generally 5 or 10 mg every 2 to 3 hours. Adequate controlled clinical studies demonstrating the effectiveness of chronic maintenance therapy with these dosage forms have not been reported.

SORBITRATE in oral doses of 10 to 40 mg given every 6 hours or in oral controlled-release doses of 40 to 80 mg given every 8 to 12 hours is generally recommended. The extent to which development of tolerance should modify the dosage program has not been defined. *The oral controlled-release forms of isosorbide dinitrate should not be chewed.*

DOSAGE FORMS AVAILABLE: Sublingual Tablets (2.5, 5, 10 mg); Chewable Tablets (5, 10 mg) Oral Tablets (5, 10, 20, 30, 40 mg); Sustained Action Tablets (40 mg)

STUART PHARMACEUTICALS
Division of ICI Americas Inc.
Wilmington, DE 19897

See following page.

Angina comes in many forms...

So does

SORBITRATE®

(ISOSORBIDE DINITRATE)

Unsurpassed flexibility in nitrate therapy.

2.5 mg 5 mg 10 mg
Sublingual Tablets

5 mg 10 mg
Chewable Tablets

5 mg 10 mg 20 mg 30 mg 40 mg
Oral "Swallow" Tablets

40 mg
Sustained Action "Swallow" Tablets

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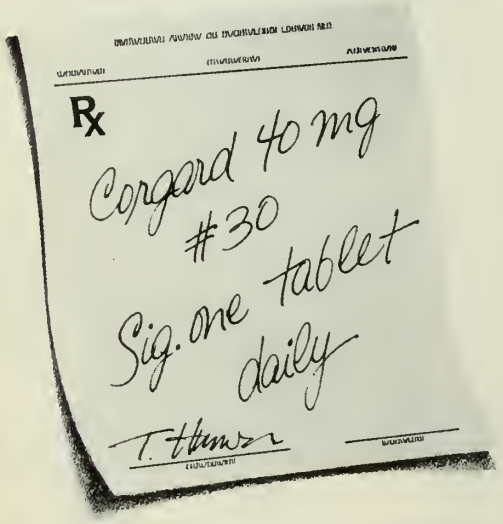
CORGARD®
(nadolol tablets)

40 mg, 80 mg, 120 mg, and 160 mg
easy-to-break scored tablets

ONCE A DAY FOR HYPERTENSION



CORGARD® TABLETS
Nadolol Tablets

DESCRIPTION: Corgard (nadolol) is a synthetic nonselective beta-adrenergic receptor blocking agent.

CONTRAINDICATIONS: Bronchial asthma, sinus bradycardia and greater than first degree conduction block, cardiogenic shock, and overt cardiac failure (see WARNINGS).

WARNINGS: Cardiac Failure–Sympathetic stimulation may be a vital component supporting circulatory function in congestive heart failure, and its inhibition by beta-blockade may precipitate more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, they can be used with caution in patients with a history of failure who are well-compensated, usually with digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle. IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta-blockers can, in some cases, lead to cardiac failure; therefore, at first sign or symptom of heart failure, digitalize and/or give diuretics, and closely observe response, or discontinue nadolol (gradually if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal–Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronic use of nadolol, particularly in patients with ischemic heart disease, gradually reduce dosage over a 1- to 2-week period and carefully monitor the patient. Reinstitute nadolol promptly (at least temporarily) and take other measures appropriate for management of unstable angina if angina markedly worsens or acute coronary insufficiency develops. Warn patients not to interrupt or discontinue therapy without physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue nadolol therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)– PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA-BLOCKERS. Administer nadolol with caution since it may block bronchodilation produced by endogenous or exogenous catecholamine stimulation of beta$_2$ receptors.

Major Surgery–Because beta blockade impairs the ability of the heart to respond to reflex stimuli and may increase risks of general anesthesia and surgical procedures, resulting in protracted hypotension or low cardiac output, it has generally been suggested that such therapy should be withdrawn several days prior to surgery. Recognition of the increased sensitivity to catecholamines of patients recently withdrawn from beta-blocker therapy, however, has made this recommendation controversial. If possible, withdraw beta-blockers well before surgery takes place. In emergency surgery, inform the anesthesiologist that the patient is on beta-blocker therapy. Use of beta-receptor agonists such as isoproterenol, dopamine, dobutamine, or levarterenol can reverse the effects of nadolol. Difficulty in restarting and maintaining the heart beat has also been reported with beta-adrenergic receptor blocking agents.

Diabetes and Hypoglycemia–Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia and blood pressure changes) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces release of insulin in response to hyperglycemia; therefore, it may be necessary to adjust dose of antidiabetic drugs.

Thyrotoxicosis–Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. To avoid abrupt withdrawal of beta-adrenergic blockade which might precipitate a thyroid storm, carefully manage patients suspected of developing thyrotoxicosis.

PRECAUTIONS: Impaired Hepatic or Renal Function–Use nadolol with caution in presence of either of these conditions (see DOSAGE AND ADMINISTRATION section of package insert).

Information for Patients–Warn patients, especially those with evidence of coronary artery insufficiency, against interruption or discontinuation of nadolol without physician's advice. Although cardiac failure rarely occurs in properly selected patients, advise patients being treated with beta-adrenergic blocking agents to consult physician at first sign or symptom of impending failure.

Drug Interactions–Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. When treating patients with nadolol plus a catecholamine-depleting agent, carefully observe for evidence of hypotension and/or excessive bradycardia which may produce vertigo, syncope, or postural hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility–In 1 to 2 years' oral toxicologic studies in mice, rats, and dogs, nadolol did not produce significant toxic effects. In 2-year oral carcinogenic studies in rats and mice, nadolol did not produce neoplastic, preneoplastic, or nonneoplastic pathologic lesions.

Pregnancy–In animal reproduction studies with nadolol, evidence of embryo-and fetotoxicity was found in rabbits (but not in rats or hamsters) at doses 5 to 10 times greater (on a mg/kg basis) than maximum indicated human dose; no teratogenic potential was seen in any of these species. There are no well-controlled studies in pregnant women; therefore, use nadolol in pregnant women only if potential benefit justifies potential risk to the fetus.

Nursing Mothers–It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when nadolol is administered to a nursing woman. Animal studies showed that nadolol is found in the milk of lactating rats.

Pediatric Use–Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects have been mild and transient and have rarely required nadolol withdrawal.

Cardiovascular–Bradycardia with heart rates of less than 60 beats per minute occurs commonly, and heart rates below 40 beats per minute and/or symptomatic bradycardia were seen in about 2 of 100 patients. Symptoms of peripheral vascular insufficiency, usually of the Raynaud type, have occurred in approximately 2 of 100 patients. Cardiac failure, hypotension, and rhythm/conduction disturbances have each occurred in about 1 of 100 patients. Single instances of first degree and third degree heart block have been reported; intensification of AV block is a known effect of beta-blockers (see also CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS). **Central Nervous System**–Dizziness or fatigue reported in approximately 2 of 100 patients; paresthesias, sedation, and change in behavior reported in approximately 6 of 1000 patients. **Respiratory**–Bronchospasm reported in approximately 1 of 1000 patients (see CONTRAINDICATIONS and WARNINGS). **Gastrointestinal**– Nausea, diarrhea, abdominal discomfort, constipation, vomiting, indigestion, anorexia, bloating, and flatulence each reported in 1 to 5 of 1000 patients. **Miscellaneous**–Each of the following reported in 1 to 5 of 1000 patients: rash; pruritus; headache; dry mouth, eyes, or skin; impotence or decreased libido; facial swelling; weight gain; slurred speech; cough; nasal stuffiness; sweating; tinnitus; blurred vision. Although relationship to drug usage is not clear, sleep disturbances have been reported. The oculomucocutaneous syndrome associated with practolol has not been reported with nadolol.

Potential Adverse Effects: Although other adverse effects reported with other beta-adrenergic blocking agents have not been reported with nadolol, they should be considered potential adverse effects of nadolol. **Central Nervous System**–reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place; short-term memory loss, emotional lability with slightly clouded sensorium; decreased performance on neuropsychometrics. **Gastrointestinal**–mesenteric arterial thrombosis; ischemic colitis. **Hematologic**–agranulocytosis; thrombocytopenic or nonthrombocytopenic purpura. **Allergic**–fever combined with aching and sore throat; laryngospasm; respiratory distress. **Miscellaneous**–reversible alopecia; Peyronie's disease; erythematous rash.

OVERDOSAGE: Nadolol can be removed from the general circulation by hemodialysis. In addition to gastric lavage, employ the following measures as appropriate. In determining duration of corrective therapy, take note of long duration of effect of nadolol.

Excessive Bradycardia–Administer atropine (0.25 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.

Cardiac Failure–Administer a digitalis glycoside and diuretic. It has been reported that glucagon may also be useful in this situation.

Hypotension–Administer vasopressors, e.g., epinephrine or levarterenol. (There is evidence that epinephrine may be the drug of choice.)

Bronchospasm–Administer a beta$_2$-stimulating agent and/or a theophylline derivative.

DOSAGE: For all patients, DOSAGE MUST BE INDIVIDUALIZED.

For **angina pectoris,** usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 mg increments at 3 to 7 day intervals until optimum clinical response or pronounced slowing of the heart rate; usual maintenance dose is 80 to 240 mg q.d. (most patients respond to 160 mg or less daily). If treatment is to be discontinued, reduce dosage gradually over a period of 1 to 2 weeks (see WARNINGS).

For **hypertension,** usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 mg increments until optimum blood pressure reduction is achieved; usual maintenance dose is 80 to 320 mg q.d. (rarely, doses up to 640 mg may be needed).

Patients with renal failure require adjustment in dosing interval; see package insert for dosage in these patients.

For full prescribing information, consult package insert.

HOW SUPPLIED: In scored tablets containing 40, 80, 120, or 160 mg nadolol per tablet in bottles of 100 and 1000 tablets and in Unimatic® unit-dose packs of 100 tablets.

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Innovators in cardiovascular medicine

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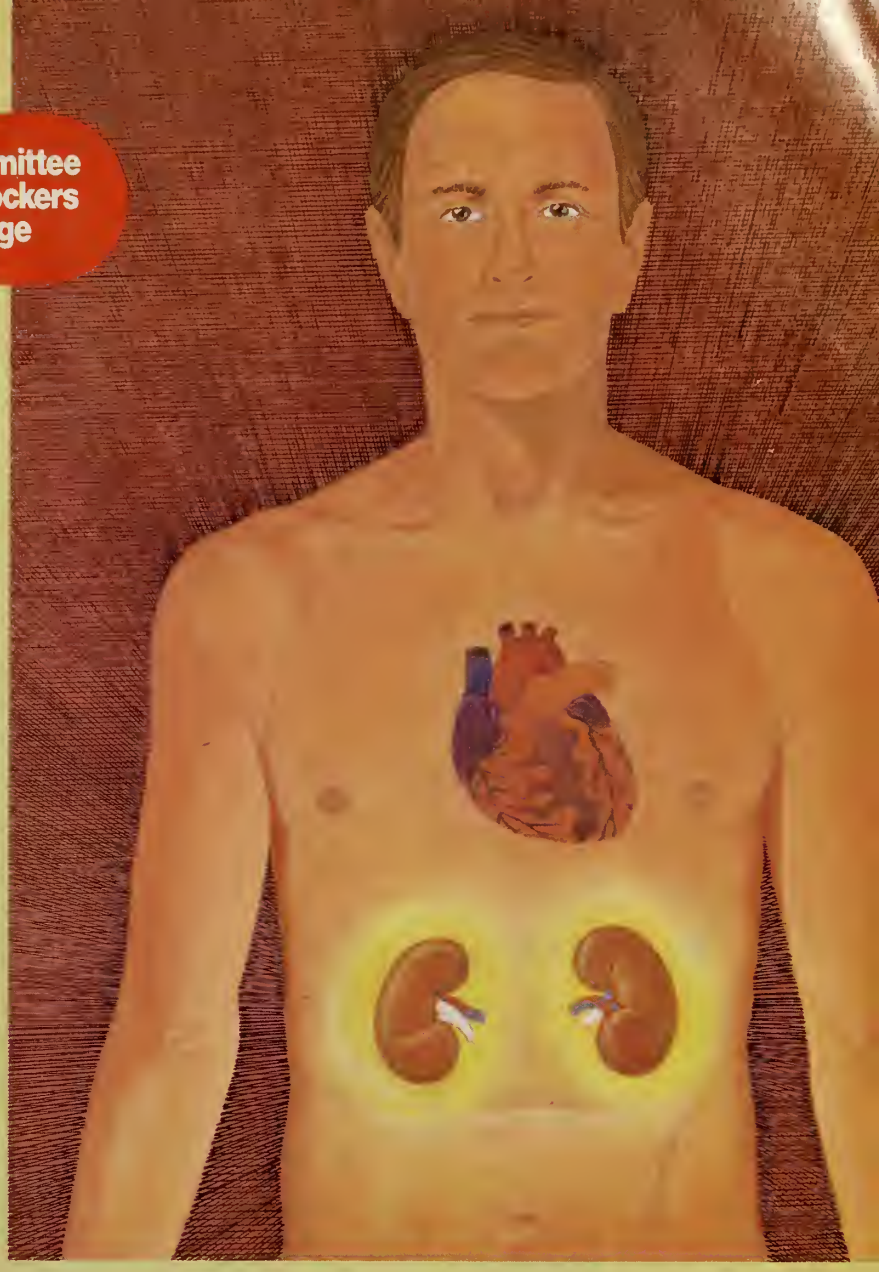
Issued: June 1984

The Joint National Committee now advocates beta-blockers for broad Step-1 usage

IN HYPERTENSION

CORGARD®
(nadolol tablets)

BLOCKS BETA RECEPTORS IN THE HEART WHILE APPARENTLY PRESERVING RENAL BLOOD FLOW



Effect on kidney

"...investigations suggest that the long-term use of nadolol, a long-acting nonselective agent, is associated with preserved renal function."[1]

"...the majority of investigators utilizing propranolol have reported decrements in RPF [renal plasma flow] and GFR [glomerular filtration rate]..."[1]

CORGARD® (nadolol tablets) should be used with caution in patients with impaired renal function.

Reference: 1. Epstein M, Oster JR: Beta-blockers and the kidney. Mineral Electrolyte Metab 8: 237-254, 1982.

SQUIBB®
Innovators in cardiovascular medicine

TAKE THE ADVANTAGE TO HEART

Please see the adjacent page of this advertisement for brief summary.

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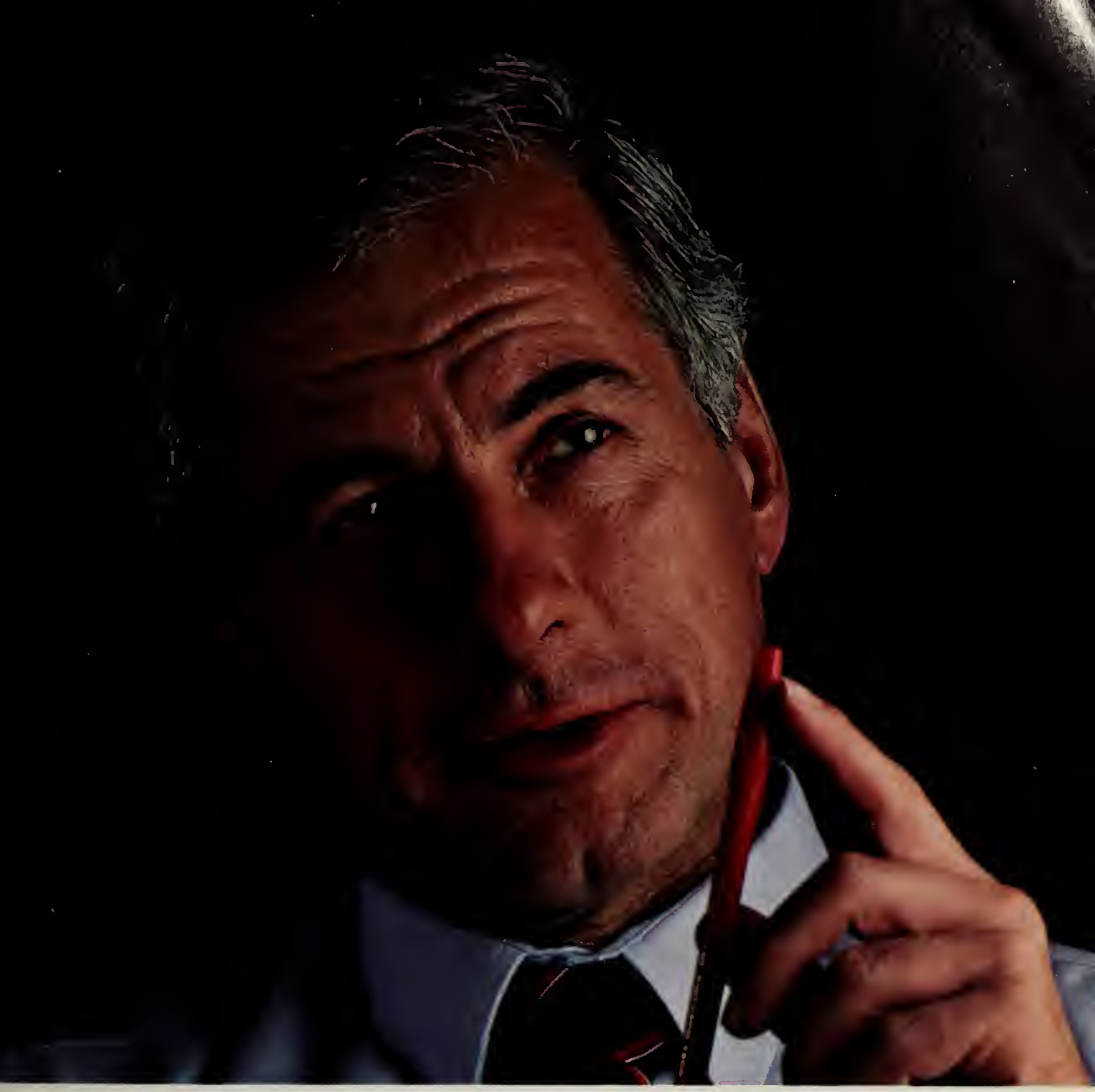


"When the Ayerst rep told me it costs about 45¢ a day, I said you can stop right there."

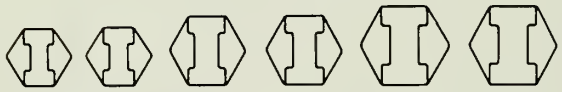
Most doctors are pleasantly surprised to learn that the average cost of daily therapy with the world's most widely used beta blocker is so little, not much more than the cost of a daily newspaper.

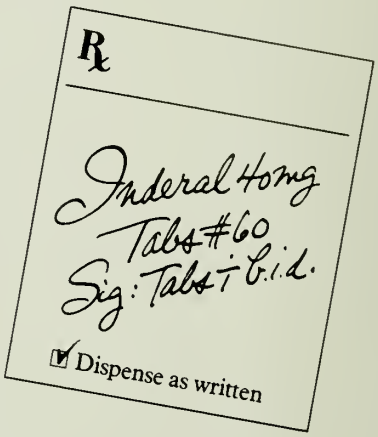
When it's INDERAL (propranolol hydrochloride) tablets you want for your hypertension patients, remember to specify Dispense As Written (DAW) or Do Not Substitute on your prescriptions. That way, you can always be assured they'll get INDERAL®. Please see next page for brief summary of prescribing information.

INDERAL®
(PROPRANOLOL HCl)
Small price to pay.

"When the Ayerst rep told me
it costs about 45¢ a day,
I said you can stop right there."

INDERAL® TABLETS
(PROPRANOLOL HCl)





BRIEF SUMMARY (FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE CIRCULAR.)

INDERAL® (propranolol hydrochloride) Tablets

CONTRAINDICATIONS

INDERAL is contraindicated in 1) cardiogenic shock, 2) sinus bradycardia and greater than first degree block, 3) bronchial asthma, 4) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL.

WARNINGS

CARDIAC FAILURE. Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta blockade may precipitate more severe failure. Although beta blockers should be avoided in overt congestive heart failure, if necessary they can be used with close follow-up in patients with a history of failure who are well compensated and are receiving digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle.

IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta blockers can, in some cases, lead to cardiac failure. Therefore, at the first sign or symptom of heart failure, the patient should be digitalized and/or treated with diuretics, and the response observed closely, or INDERAL should be discontinued (gradually, if possible).

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following abrupt discontinuance of INDERAL therapy. Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced over at least a few weeks and the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)—PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

MAJOR SURGERY: The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

INDERAL, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in starting and maintaining the heartbeat has also been reported with beta blockers.

DIABETES AND HYPOGLYCEMIA: Beta-adrenergic blockade may prevent the appearance of certain premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia in labile insulin-dependent diabetes. In these patients, it may be more difficult to adjust the dosage of insulin.

THYROTOXICOSIS: Beta blockade may mask certain clinical signs of hyperthyroidism. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

PRECAUTIONS

General: Propranolol should be used with caution in patients with impaired hepatic or renal function. INDERAL is not indicated for the treatment of hypertensive emergencies.

Beta-adrenoreceptor blockade can cause reduction of intraocular pressure. Patients should be told that INDERAL (propranolol hydrochloride) may interfere with the glaucoma screening test. Withdrawal may lead to a return of increased intraocular pressure.

Clinical Laboratory Tests: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

DRUG INTERACTIONS: Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if INDERAL is administered. The added catecholamine-blocking action may produce an excessive reduction of resting sympathetic nervous activity which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In 18-month studies in both rats and mice, employing doses up to 150 mg/kg/day, there was no evidence of significant drug-induced toxicity. There were no drug-related tumorigenic effects at any of the dosage levels. Reproductive studies in animals did not show any impairment of fertility that was attributable to the drug.

Pregnancy: Pregnancy Category C. INDERAL has been shown to be embryotoxic in animal studies at doses about 10 times greater than the maximum recommended human dose.

There are no adequate and well-controlled studies in pregnant women. INDERAL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: INDERAL is excreted in human milk. Caution should be exercised when INDERAL is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Most adverse effects have been mild and transient and have rarely required the withdrawal of therapy.

Cardiovascular: bradycardia; congestive heart failure; intensification of AV block; hypotension; paresthesia of hands; thrombocytopenic purpura; arterial insufficiency, usually of the Raynaud type.

Central Nervous System: Lightheadedness; mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Gastrointestinal: nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis.

Allergic: pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Respiratory: bronchospasm.

Hematologic: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Auto-Immune: In extremely rare instances, systemic lupus erythematosus has been reported.

Miscellaneous: alopecia, LE-like reactions, psoriasiform rashes, dry eyes, male impotence, and Peyronie's disease have been reported rarely. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been associated with propranolol.

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New York, N.Y. 10017

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Continuing Medical Education

CALIFORNIA, HAWAII, NEVADA • ALASKA • IDAHO • MONTANA • NEW MEXICO • OREGON • UTAH • WASHINGTON • WYOMING

CALIFORNIA, HAWAII AND NEVADA

This listing of continuing education programs in California, Hawaii and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Department of Continuing Medical Education, California Medical Association, 44 Gough St., San Francisco 94103; or phone (415) 863-5522. For a list of organizations approved for Category I credit toward the CMA Certificate in Continuing Medical Education or for more information on accreditation or certification, please write to the above address.

ALLERGY AND IMMUNOLOGY

February 27-March 2—**9th Annual Course: Immunology and the Clinical Practice of Allergy.** UCSD at Vacation Village Resort, San Diego. Wednesday-Sunday. Up to 20 hrs. Contact: UCSD.

March 18-20—**Problem Areas in the Immunization Cycle.** American College of Preventitive Medicine at San Diego. Monday-Wednesday. Contact: National Council for International Health, 2100 Pennsylvania Ave. N.W., Ste. 740, Washington, DC 20073.

April 18-20—**Allergy and Immunology for the Practicing Physician.** UCSF. Thursday-Saturday. 18 hrs. Fee: $200.

ANESTHESIOLOGY

January 25-27—**23rd Annual Clinical Conference in Pediatric Anesthesiology.** Pediatric Anesthesiology Foundation and Childrens Hospital of Los Angeles at Los Angeles. Friday-Sunday. Contact: Wayne Herbert, MD, Program Dir., Ped. Anes. Fndn., PO Box 54700, Los Angeles 90054. (213) 669-2262.

CANCER

January 18-19—**Urological Cancer.** USC. Friday-Saturday.

January 19—**Avoidable Cancer: Cause and Control.** UCI. Saturday. 6 hrs. Fee: $30. Contact: UCI.

February 6—**Impact of Questionable Cancer: Treatments on Oncology Practice Today.** Hospital of Good Samaritan at Biltmore Hotel, Los Angeles. Wednesday. 6 hrs. Contact: Dolores Gay, Coordinator of Symposium, 616 S. Witmer St., Los Angeles 90017. (213) 977-2352.

February 14-16—**Annual Oncology Review.** UCLA at Century Plaza Hotel. Thursday-Saturday. 20 hrs.

March 1-2—**Cancer and the Elderly.** West Coast Cancer Foundation at Sheraton Palace Hotel, San Francisco. Friday-Saturday. 12 hrs. Fee: $150. Contact: West Coast Cancer Foundation, 50 Francisco, San Francisco 94133.

March 22—**One Day Cancer Screening and Flexible Sigmoidoscopy Workshop.** Continuing Medical Education Associates at Holiday Inn Union Square, San Francisco. Friday. 7 hrs. Fee: $135. Contact: J. Shiller. CMEA, PO Box 84296, San Diego 92138.

(Continued on Page 22)

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 44 Gough Street, San Francisco 94103. (415) 863-5522.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Flora Harlee-Cordett, MS, MPH, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr., MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, ext. 2400.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 563-4321, ext. 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 497-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0328.

UCI: University of California, Irvine
Contact: E. R. Jennings, MD, Assistant Dean, University of California, Irvine, California College of Medicine, c/o UCI/CME Program, Memorial Hospital Medical Center, 2801 Atlantic Avenue, Long Beach 90801. (213) 595-3837, or (714) 856-5414, UCI Extension.

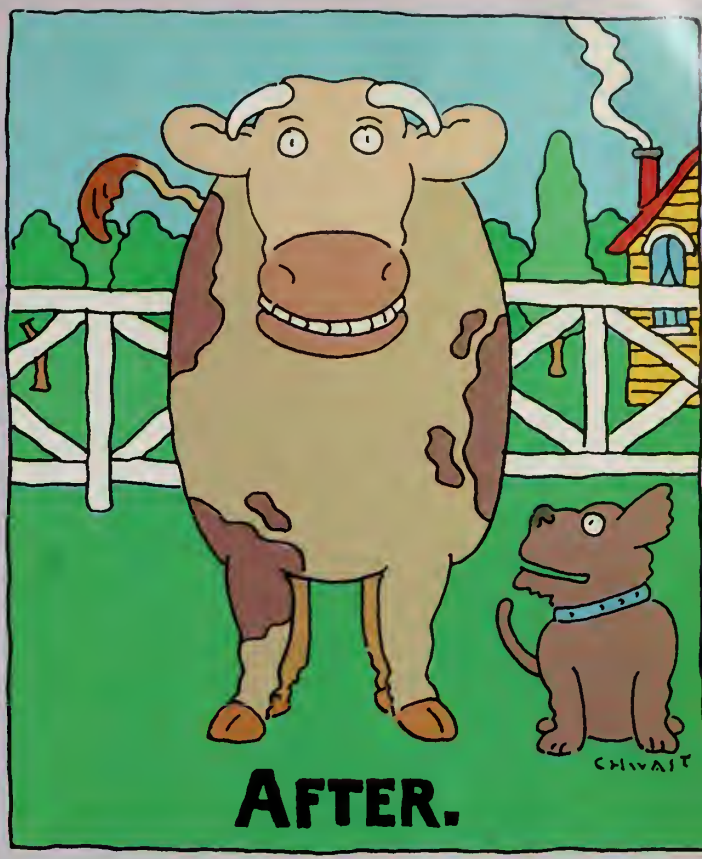
UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 452-3940.

UCSF: University of California, San Francisco
Contact: David S. Gullion, MD, Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 224-7051.

"My great, great, great, great grand daddy."



"Slim, trim, wonderful me."

"HOW I LOST MY UGLY FAT."

Years ago, you couldn't find one of my relatives that didn't have a rump that really rolled.

Of course, for years people said they liked us that way.

But then my great, great, great grandmother met an incredibly well-built bull. Just about everything that guy ate turned to good lean muscle. The whole family hasn't been the same since.

Today we're down to a mere nine grams of fat per three-ounce portion. And over half of it's unsaturated. Plus that serving has 192 calories, no more cholesterol than roast chicken without the skin, and all kinds of iron, zinc, B-vitamins and protein.*

Why, we're even longer and taller than ever before.

In fact, just the other night I met a nutritionist for dinner. And he said that I never looked better.

For a great free recipe booklet featuring lots of lean and low calorie cooking with beef, send your name and address to:

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*Beef data from 1983 Beef Nutritive Composition Studies conducted by the U.S.D.A. and National Live Stock and Meat Board.

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Make Land With All Speed

for California Medical Association's 114th Annual Session
March 8-13, 1985
Town and Country Hotel, San Diego

Art: National Maritime Museum

Exciting Ports-Of-Call Await

Annual Scientific Assembly

Chart your course through the exciting cross-currents of modern medicine. Over 40 scientific and educational programs have been logged, including dozens of lectures, panels and workshops on subjects of vital interest to physicians of all specialties. Category I Credit is approved for most programs.

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Be on deck when CMA's 423 member policymaking body convenes to debate the critical political, scientific and socioeconomic issues confronting California physicians.

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Cruise, again and again, through an exhibit hall filled with fascinating and informative exhibits, over 180 commercial and scientific displays in all, from around the state and across the nation.

Special Events

When at liberty, sample the slate of eleven sensational special events created for physician and family alike.

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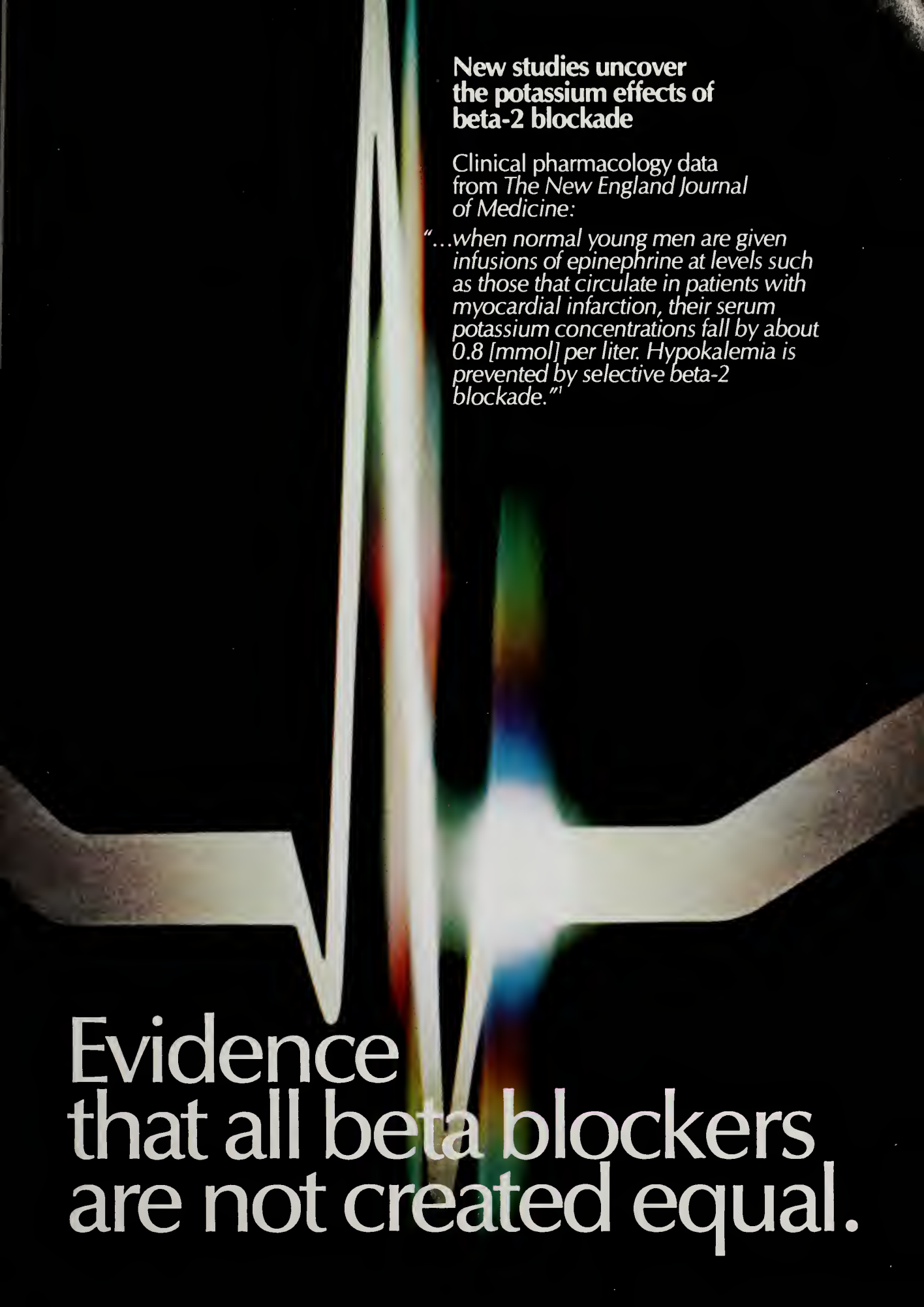


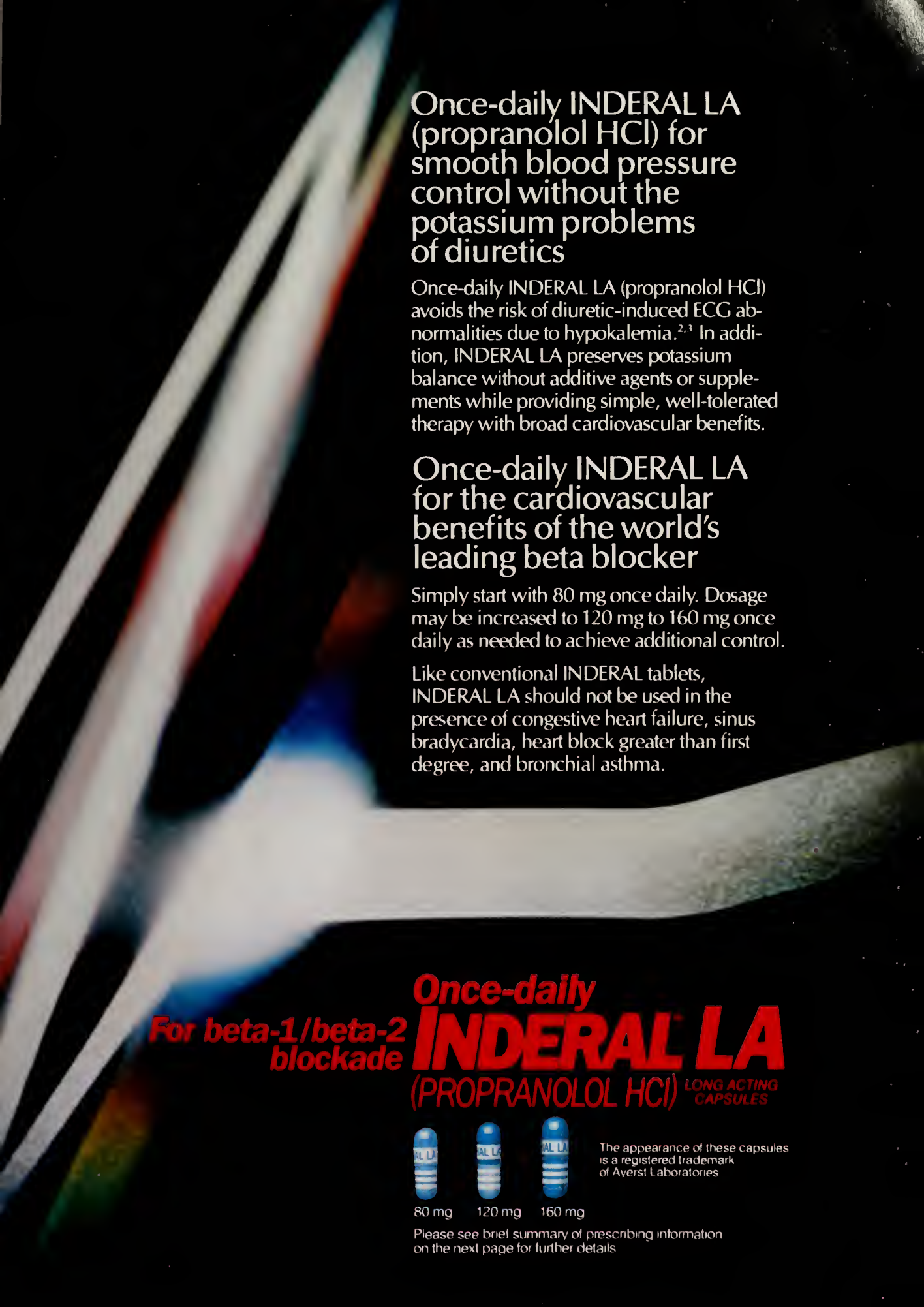
New studies uncover the potassium effects of beta-2 blockade

Clinical pharmacology data from *The New England Journal of Medicine:*

"...when normal young men are given infusions of epinephrine at levels such as those that circulate in patients with myocardial infarction, their serum potassium concentrations fall by about 0.8 [mmol] per liter. Hypokalemia is prevented by selective beta-2 blockade."[1]

Evidence that all beta blockers are not created equal.

Right from the start in hypertension...



Once-daily INDERAL LA (propranolol HCl) for smooth blood pressure control without the potassium problems of diuretics

Once-daily INDERAL LA (propranolol HCl) avoids the risk of diuretic-induced ECG abnormalities due to hypokalemia.[2,3] In addition, INDERAL LA preserves potassium balance without additive agents or supplements while providing simple, well-tolerated therapy with broad cardiovascular benefits.

Once-daily INDERAL LA for the cardiovascular benefits of the world's leading beta blocker

Simply start with 80 mg once daily. Dosage may be increased to 120 mg to 160 mg once daily as needed to achieve additional control.

Like conventional INDERAL tablets, INDERAL LA should not be used in the presence of congestive heart failure, sinus bradycardia, heart block greater than first degree, and bronchial asthma.

For beta-1/beta-2 blockade

Once-daily

INDERAL® LA

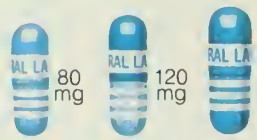
(PROPRANOLOL HCl) LONG ACTING CAPSULES

80 mg 120 mg 160 mg

The appearance of these capsules is a registered trademark of Ayerst Laboratories

Please see brief summary of prescribing information on the next page for further details

Once-daily For beta-1/beta-2 blockade INDERAL® LA (PROPRANOLOL HCl) LONG ACTING CAPSULES



The appearance of these capsules is a registered trademark of Ayerst Laboratories

BRIEF SUMMARY *(FOR FULL PRESCRIBING INFORMATION SEE PACKAGE CIRCULAR.)*

INDERAL® LA brand of propranolol hydrochloride **(Long Acting Capsules)**

DESCRIPTION. Inderal LA is formulated to provide a sustained release of propranolol hydrochloride. Inderal LA is available as 80 mg, 120 mg, and 160 mg capsules.

CLINICAL PHARMACOLOGY. INDERAL is a nonselective beta-adrenergic receptor blocking agent possessing no other autonomic nervous system activity. It specifically competes with beta-adrenergic receptor stimulating agents for available receptor sites. When access to beta-receptor sites is blocked by INDERAL, the chronotropic, inotropic, and vasodilator responses to beta-adrenergic stimulation are decreased proportionately.

INDERAL LA Capsules (80, 120, and 160 mg) release propranolol HCl at a controlled and predictable rate. Peak blood levels following dosing with INDERAL LA occur at about 6 hours and the apparent plasma half-life is about 10 hours. When measured at steady state over a 24-hour period the areas under the propranolol plasma concentration-time curve (AUCs) for the capsules are approximately 60% to 65% of the AUCs for a comparable divided daily dose of INDERAL tablets. The lower AUCs for the capsules are due to greater hepatic metabolism of propranolol, resulting from the slower rate of absorption of propranolol. Over a twenty-four (24) hour period, blood levels are fairly constant for about twelve (12) hours then decline exponentially.

INDERAL LA should not be considered a simple mg for mg substitute for conventional propranolol and the blood levels achieved do not match (are lower than) those of two to four times daily dosing with the same dose. When changing to INDERAL LA from conventional propranolol, a possible need for retitration upwards should be considered especially to maintain effectiveness at the end of the dosing interval. In most clinical settings, however, such as hypertension or angina where there is little correlation between plasma levels and clinical effect, INDERAL LA has been therapeutically equivalent to the same mg dose of conventional INDERAL as assessed by 24-hour effects on blood pressure and on 24-hour exercise responses of heart rate, systolic pressure and rate pressure product. INDERAL LA can provide effective beta blockade for a 24-hour period.

The mechanism of the antihypertensive effect of INDERAL has not been established. Among the factors that may be involved in contributing to the antihypertensive action are (1) decreased cardiac output, (2) inhibition of renin release by the kidneys, and (3) diminution of tonic sympathetic nerve outflow from vasomotor centers in the brain. Although total peripheral resistance may increase initially, it readjusts to or below the pretreatment level with chronic use. Effects on plasma volume appear to be minor and somewhat variable. INDERAL has been shown to cause a small increase in serum potassium concentration when used in the treatment of hypertensive patients.

In angina pectoris, propranolol generally reduces the oxygen requirement of the heart at any given level of effort by blocking the catecholamine-induced increases in the heart rate, systolic blood pressure, and the velocity and extent of myocardial contraction. Propranolol may increase oxygen requirements by increasing left ventricular fiber length, end diastolic pressure and systolic ejection period. The net physiologic effect of beta-adrenergic blockade is usually advantageous and is manifested during exercise by delayed onset of pain and increased work capacity.

In dosages greater than required for beta blockade, INDERAL also exerts a quinidine-like or anesthetic-like membrane action which affects the cardiac action potential. The significance of the membrane action in the treatment of arrhythmias is uncertain.

The mechanism of the antimigraine effect of propranolol has not been established. Beta-adrenergic receptors have been demonstrated in the pial vessels of the brain.

Beta receptor blockade can be useful in conditions in which, because of pathologic or functional changes, sympathetic activity is detrimental to the patient. But there are also situations in which sympathetic stimulation is vital. For example, in patients with severely damaged hearts, adequate ventricular function is maintained by virtue of sympathetic drive which should be preserved. In the presence of AV block, greater than first degree, beta blockade may prevent the necessary facilitating effect of sympathetic activity on conduction. Beta blockade results in bronchial constriction by interfering with adrenergic bronchodilator activity which should be preserved in patients subject to bronchospasm.

Propranolol is not significantly dialyzable.

INDICATIONS AND USAGE. Hypertension: INDERAL LA is indicated in the management of hypertension, it may be used alone or used in combination with other antihypertensive agents, particularly a thiazide diuretic. INDERAL LA is not indicated in the management of hypertensive emergencies.

Angina Pectoris Due to Coronary Atherosclerosis: INDERAL LA is indicated for the long-term management of patients with angina pectoris.

Migraine: INDERAL LA is indicated for the prophylaxis of common migraine headache. The efficacy of propranolol in the treatment of a migraine attack that has started has not been established and propranolol is not indicated for such use.

Hypertrophic Subaortic Stenosis: INDERAL LA is useful in the management of hypertrophic subaortic stenosis, especially for treatment of exertional or other stress-induced angina, palpitations, and syncope. INDERAL LA also improves exercise performance. The effectiveness of propranolol hydrochloride in this disease appears to be due to a reduction of the elevated outflow pressure gradient which is exacerbated by beta-receptor stimulation. Clinical improvement may be temporary.

CONTRAINDICATIONS. INDERAL is contraindicated in 1) cardiogenic shock, 2) sinus bradycardia and greater than first degree block, 3) bronchial asthma, 4) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL.

WARNINGS. CARDIAC FAILURE. Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta blockade may precipitate more severe failure. Although beta blockers should be avoided in overt congestive heart failure, if necessary they can be used with close follow-up in patients with a history of failure who are well compensated and are receiving digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle.

IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta blockers can, in some cases, lead to cardiac failure. Therefore, at the first sign or symptom of heart failure, the patient should be digitalized and/or treated with diuretics, and the response observed closely; or INDERAL should be discontinued (gradually if possible).

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following abrupt discontinuance of INDERAL therapy. Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced over at least a few weeks, and the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)—PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

MAJOR SURGERY. The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

INDERAL (propranolol HCl), like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in starting and maintaining the heartbeat has also been reported with beta blockers.

DIABETES AND HYPOGLYCEMIA. Beta-adrenergic blockade may prevent the appearance of certain premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia in labile insulin-dependent diabetes. In these patients, it may be more difficult to adjust the dosage of insulin.

THYROTOXICOSIS. Beta blockade may mask certain clinical signs of hyperthyroidism. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

PRECAUTIONS. *General.* Propranolol should be used with caution in patients with impaired hepatic or renal function. INDERAL (propranolol HCl) is not indicated for the treatment of hypertensive emergencies.

Beta adrenoreceptor blockade can cause reduction of intraocular pressure. Patients should be told that INDERAL may interfere with the glaucoma screening test. Withdrawal may lead to a return of increased intraocular pressure.

Clinical Laboratory Tests. Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

DRUG INTERACTIONS. Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if INDERAL is administered. The added catecholamine-blocking action may produce an excessive reduction of resting sympathetic nervous activity which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility. Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In 18-month studies in both rats and mice, employing doses up to 150 mg/kg/day, there was no evidence of significant drug-induced toxicity. There were no drug-related tumorigenic effects at any of the dosage levels. Reproductive studies in animals did not show any impairment of fertility that was attributable to the drug.

Pregnancy. Pregnancy Category C. INDERAL has been shown to be embryotoxic in animal studies at doses about 10 times greater than the maximum recommended human dose.

There are no adequate and well-controlled studies in pregnant women. INDERAL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. INDERAL is excreted in human milk. Caution should be exercised when INDERAL is administered to a nursing woman.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS. Most adverse effects have been mild and transient and have rarely required the withdrawal of therapy.

Cardiovascular. bradycardia, congestive heart failure, intensification of AV block, hypotension, paresthesia of hands, thrombocytopenic purpura, arterial insufficiency, usually of the Raynaud type.

Central Nervous System. lightheadedness, mental depression manifested by insomnia, lassitude, weakness, fatigue, reversible mental depression progressing to catatonia, visual disturbances, hallucinations, an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Gastrointestinal. nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis.

Allergic. pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Respiratory. bronchospasm.

Hematologic. agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Auto-Immune. In extremely rare instances, systemic lupus erythematosus has been reported.

Miscellaneous. alopecia, LE-like reactions, psoriasiform rashes, dry eyes, male impotence, and Peyronie's disease have been reported rarely. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been associated with propranolol.

DOSAGE AND ADMINISTRATION. INDERAL LA provides propranolol hydrochloride in a sustained-release capsule for administration once daily. If patients are switched from INDERAL tablets to INDERAL LA capsules, care should be taken to assure that the desired therapeutic effect is maintained. INDERAL LA should not be considered a simple mg for mg substitute for INDERAL. INDERAL LA has different kinetics and produces lower blood levels. Retitration may be necessary especially to maintain effectiveness at the end of the 24-hour dosing interval.

HYPERTENSION—*Dosage must be individualized.* The usual initial dosage is 80 mg INDERAL LA once daily, whether used alone or added to a diuretic. The dosage may be increased to 120 mg once daily or higher until adequate blood pressure control is achieved. The usual maintenance dosage is 120 to 160 mg once daily. In some instances a dosage of 640 mg may be required. The time needed for full hypertensive response to a given dosage is variable and may range from a few days to several weeks.

ANGINA PECTORIS—*Dosage must be individualized.* Starting with 80 mg INDERAL LA once daily, dosage should be gradually increased at three to seven day intervals until optimum response is obtained. Although individual patients may respond at any dosage level, the average optimum dosage appears to be 160 mg once daily. In angina pectoris the value and safety of dosage exceeding 320 mg per day have not been established.

If treatment is to be discontinued, reduce dosage gradually over a period of a few weeks (see WARNINGS).

MIGRAINE—*Dosage must be individualized.* The initial oral dose is 80 mg INDERAL LA once daily. The usual effective dose range is 160-240 mg once daily. The dosage may be increased gradually to achieve optimum migraine prophylaxis. If a satisfactory response is not obtained within four to six weeks after reaching the maximum dose, INDERAL LA therapy should be discontinued. It may be advisable to withdraw the drug gradually over a period of several weeks.

HYPERTROPHIC SUBAORTIC STENOSIS—80-160 mg INDERAL LA once daily.

PEDIATRIC DOSAGE. At this time the data on the use of the drug in this age group are too limited to permit adequate directions for use.

REFERENCES

1. Epstein FH, Rosa RM. Adrenergic control of serum potassium. *N Engl J Med* 1983; 309:1450-1451. **2.** Holland OB, Nixon JV, Kuhnert L. Diuretic-induced ventricular ectopic activity. *Am J Med* 1981; 70:762-768. **3.** Holme I, Helgeland A, Hjermann I, et al. Treatment of mild hypertension with diuretics. The importance of ECG abnormalities in the Oslo study and in MRFIT. *JAMA* 1984;251:1298-1299.

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See brief summary of prescribing information on next page.

ZORprin (aspirin) ZERO-ORDER RELEASE

Before prescribing see complete prescribing information. The following is a brief summary. ▫ **INDICATIONS AND USE**: ZORprin® is indicated for the treatment of rheumatoid arthritis and osteoarthritis. The safety and efficacy of ZORprin® have not been established in those rheumatoid arthritic patients who are designated by the American Rheumatism Association as Functional Class IV, (incapacitated, largely or wholly bedridden, or confined to wheelchair, little or no self-care). ▫ **CONTRAINDICATIONS**: ZORprin® should not be used in patients known to be hypersensitive to salicylates or in individuals with the syndrome of nasal polyps, angioedema, bronchospastic reactivity to aspirin, renal or hepatic insufficiency, hypoprothrombinemia or other bleeding disorders. ZORprin® is not recommended for children under 12 years of age; it is contraindicated in all children with fever accompanied by dehydration. ▫ **WARNINGS**: ZORprin® should be used with caution when anticoagulants are prescribed concurrently, since aspirin may depress the concentration of prothrombin in plasma and increase bleeding time. Large doses of salicylates may have hypoglycemic action and enhance the effect of the oral hypoglycemics; concomitant use therefore is not recommended. However, if such use is necessary, dosage of the hypoglycemic agent must be reduced. The hypoglycemic action of the salicylates may also necessitate adjustment of the insulin requirements of diabetics. While salicylates in large doses have a uricosuric effect, smaller amounts may reduce the uricosuric effect of uricosuric agents. ▫ **USE IN PREGNANCY**: Aspirin can cause fetal harm when administered to pregnant women. Aspirin interferes with maternal and infant blood clotting and may lengthen the duration of pregnancy and parturition. Aspirin has produced teratogenic effects and increases the incidence of stillbirths and neonatal deaths in animals. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Aspirin should not be taken during the last 3 months of pregnancy. ▫ **PRECAUTIONS**: Appropriate precautions should be taken in prescribing ZORprin® for patients who are known to be sensitive to aspirin or salicylates. Particular care should be used when prescribing this medication for patients with erosive gastritis, peptic ulcer, mild diabetes or gout. As with all salicylate drugs, caution should be exercised in prescribing ZORprin® for those patients with bleeding tendencies or those on anticoagulant drugs. Large doses of salicylates should be avoided in patients with clear evidence of carditis. In order to avoid exacerbation of disease or adrenal insufficiency, patients who have been on prolonged corticosteroid therapy should have their therapy tapered slowly rather than discontinued abruptly when ZORprin® (aspirin) is made a part of the treatment program. Patients receiving large doses of aspirin and/or prolonged therapy may develop mild salicylate intoxication (salicylism) that may be reversed by reduction in dosage. Salicylates can produce changes in thyroid function tests. Salicylates should be used with caution in patients with severe hepatic damage, preexisting hypoprothrombinemia, Vitamin K deficiency and in those undergoing surgery. Since aspirin release from ZORprin® is pH dependent, it may change in those conditions where the gastric pH has been increased via antacids, gastric secretion inhibitors or surgical procedures. ▫ **ADVERSE REACTIONS**: **Hematologic**: Aspirin interferes with blood clotting. Patients with a history of blood coagulation defects or receiving anti-coagulant drugs or with severe anemia should avoid ZORprin®. Aspirin used chronically may cause a persistent iron deficiency anemia. **Gastrointestinal**: Aspirin may potentiate peptic ulcer, and cause stomach distress or heartburn. Aspirin can cause an increase in occult bleeding and in some patients massive gastrointestinal bleeding. However, the greatest release of active drug from ZORprin® is designed to occur in the small intestine over a period of time. This has resulted in less symptomatic gastrointestinal side effects. **Allergic**: Allergic and anaphylactic reactions have been noted when hypersensitive individuals have taken aspirin. The most common allergic reaction to aspirin is the induction of bronchospasm with asthma-like symptoms. Other reactions are hives, rash, angioedema, as well as rhinitis and nasal polyps. Fatal anaphylactic shock, while not common, has been reported. **Central Nervous System**: Taken in overdoses, aspirin provides stimulation which may be manifested by tinnitus. Following initial stimulation, depression of the central nervous system may be noted. **Renal**: Aspirin may rarely cause an increase in the severity of chronic kidney disease. **Hepatic**: High doses of aspirin have been reported to produce reversible hepatic dysfunction. ▫ **OVERDOSAGE**: Overdosage, if it occurs, would produce the usual symptoms of salicylism, tinnitus, vertigo, headache, confusion, drowsiness, sweating, hyperventilation, vomiting or diarrhea. Treatment for mild intoxication, emptying the stomach with an emetic, or gastric lavage with 5% sodium bicarbonate. Individuals suffering from severe intoxication should, in addition, have forced diuresis by intravenous infusions of saline and sodium bicarbonate or sodium lactate, dextrose solution. In extreme cases, hemodialysis or peritoneal dialysis may be required. ▫ **HOW SUPPLIED**: ZORprin® tablets 800 mg, plain, white capsule-shaped tablets. Bottles of 100 tablets. ▫ **CAUTION**: Federal Law prohibits dispensing without prescription. Manufactured and distributed by Boots Pharmaceuticals, Inc., Shreveport, LA, 71106 USA.

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(Continued from Page 14)

March 24—**One Day Colon Cancer Screening and Flexible Sigmoidoscopy.** Continuing Medical Education Associates at Kona Kai Club, San Diego, Sunday. 7 hrs. Fee: $135. Contact: J. Shiller, CMEA, PO Box 84296, San Diego 92138.

April 6-8—**Diagnosis and Management of the Malignant Melanoma.** UCSF. Thursday-Saturday. 11 hrs. Fee: $250.

CARDIOLOGY

January 18-19—**4th Clinical Conference on Congenital Heart Disease.** Childrens Hospital of Los Angeles at Sheraton Grande Hotel, Los Angeles. Friday-Saturday. 10 hrs. Contact: Masato Takahasi, MD, Division of Cardiology, Childrens Hospital of Los Angeles, PO Box 54700, Los Angeles 90054-0700. (213) 669-2461.

January 25-27—**Vascular and Pulmonary Disease: Diagnosis and Management.** University of Colorado Health Sciences Center at MGM Grand Hotel, Las Vegas. Friday-Sunday. 13 hrs. Contact: Med. Ed. Resources, 5808 S. Rapp St., Ste. 202, Littleton, CO 80120. (800) 421-3756.

January 28-31—**3rd Annual Cardiology Update.** Institute for Medical Studies at Sheraton-Waikiki, Hawaii. Monday-Thursday. 15 hrs. Fee: $395. Contact: Kim Stroich, Institute for Medical Studies, 30131 Town Center Rd., Ste. 215, Laguna Miguel, CA 92677. (714) 495-4499.

February 8-10—**"Case Studies in Cardiology": A Cardiology Review for Clinicians.** The Presbyterian Heart Institute at Presbyterian Hospital, Albuquerque, NM. Friday-Sunday. 19 hrs. Fee: $150. Contact: Gilbert Raff, MD, (505) 242-2796.

February 9—**"Ischemic Mitral Regurgitation" Cardiac Lecture Series.** Heart Institute of the Desert at Annenberg Health Center, Rancho Mirage. Saturday. 2 hrs. Contact: Eisenhower Medical Center, 39000 Bob Hope Dr., Rancho Mirage, CA 92270. (619) 568-2900.

February 15-17—**Vascular and Pulmonary Diseases: Diagnosis and Management.** University of Colorado Health Sciences Center at International Hotel, Palm Springs. Friday-Sunday. 13 hrs. Contact: Medical Education Resources, 5808 S. Rapp St., Ste. 202, Littleton, CO 80120. (800) 421-3756.

February 22-24—**Coronary Artery Disease and Sudden Death: Primary and Secondary Prevention.** International Medical Education Corp. at Americana Canyon, Palm Springs. Friday-Sunday. 13 hrs. Fee: $295. Contact: IMEC, 64 Inverness Dr. E, Englewood, CO 80112.

March 1-3—**ECG Interpretation and Arrhythmia Management.** International Medical Corp. at Desert Inn, Las Vegas. Friday-Sunday. 13 hrs. Fee: $295. Contact: IMEC, 64 Inverness Dr. E, Englewood, CO 80112.

March 6-8—**2nd Annual Professional Symposium on Acute Cardiopulmonary Disease.** Mercy Hospital of Sacramento at Ahwahnee Hotel, Yosemite. Wednesday-Friday. 13 hrs. Contact Joan Willis, Mercy Hospital, (916) 456-3365.

March 10-14—**34th Annual Scientific Session of the American College of Cardiology** at Anaheim. Sunday-Thursday. Contact: ACC, 9111 Old Georgetown Rd., Bethesda, MD 20814, (301) 897-5400.

March 13—**Cardiology: Arrhythmias—Recognition and Treatment.** LLU. Wednesday. 4 hrs.

March 16—**Cardiac Lecture Series: "Cardiovascular Trauma Texas Style."** Heart Institute of the Desert at Annenberg Center, Rancho Mirage. Saturday. 2 hrs. Contact: Eisenhower Medical Center, 39000 Bob Hope Dr., Rancho Mirage, CA 92270.

March 22-24—**Cardiology for the Primary Care Physician.** UCSD at Palm Springs Spa Hotel. Friday-Sunday. 18 hrs.

March 25-29—**Vascular and Pulmonary Diseases: Diagnosis & Management.** Medical Education Resources at Sheraton Maui, HI. 13 hrs. Fee: $275. Contact: Leslie Shaffer, Medical Education Resources, 5808 S. Rapp St., Ste 202, Littleton, CO 80120. (303) 798-9682.

March 29-31—**Vascular and Pulmonary Disease: Diagnosis and Management.** University of Colorado at Desert Inn, Las Vegas. Friday-Sunday. 13 hrs. Contact: Medical Education Resources, 5808 S. Rapp St., Ste. 202, Littleton, CO 80120. (800) 421-3756.

April 6—**Cardiac Lecture Series: The Ideal Conduit.** Heart Institute of the Desert at Annenberg Center, Rancho Mirage. Saturday. 2 hrs. Contact: Eisenhower Medical Center, 39000 Bob Hope Dr., Rancho Mirage 92270.

April 10-13—**1st Annual Program—Two Dimensional Echocardiography: Core Curriculum and Self-Assessment.** American College of Cardiology at Sheraton Harbor Island East, San Diego. Wednesday-Saturday. Contact: ACC, 9111 Old Georgetown Rd., Bethesda, MD 20814.

April 15-19—**ECG Interpretation and Arrhythmia Management.** International Medical Education Corp. at Marriott Hotel, Maui. Monday-Friday. 13

(Continued on Page 26)

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New study reveals no interaction betwee Ativan® (lorazepam) and Darvon® (propoxyphene HCl) Ⓒ Ⓒ Ⓒ Ⓒ

In a study evaluating the influence of propoxyphene coadministration on the pharmacokinetics of the oxidatively metabolized benzodiazepines Xanax® (alprazolam) Ⓒ and Valium® (diazepam) Ⓒ, and a benzodiazepine metabolized by conjugation, Ativan® (lorazepam), the following results were reported:

with Xanax, propoxyphene caused a large and highly significant prolongation of half-life and impairment of total metabolic clearance.[1]

in the case of Valium, propoxyphene produced a small but not statistically significant impairment of clearance.[1]

propoxyphene had no apparent effect on the distribution, half-life or clearance of Ativan.[1]

In this randomized crossover study, eight healthy male and female volunteers received single oral doses of alprazolam (1 mg), six received single IV doses of diazepam (10 mg), and five received single IV doses of lorazepam (2 mg), once in a drug-free control state and again during coadministration of propoxyphene (65 mg q6h). Consistent with previous findings, this study evidences that Ativan does not interact with drugs that undergo oxidative metabolism.[2-5] In contrast to most other benzodiazepines, Ativan does not compete for the cytochrome P-450 enzyme system.

The clinical implications of the pharmacokinetic interaction, or non-interaction, of propoxyphene with benzodiazepines are not established by this study. Even without a pharmacokinetic interaction, propoxyphene and benzodiazepines share central depressant properties and therefore should be coadministered with suitable caution. A concurrent pharmacokinetic interaction indicates a need for even further caution. Coadministration of propoxyphene and alprazolam, for example, would produce not only the expected pharmacodynamic interaction, but also whatever additional central depressant effect would be produced by the elevated steady-state plasma concentrations of alprazolam due to its impaired clearance.

Caution should also be observed when propoxyphene is prescribed for patients who use alcohol to excess.

References

1. Abernethy DR, Greenblatt DJ, Shader RI: Data on file, Wyeth Laboratories.
2. Palwardhan RV, Yarborough GW, Desmond PV, et al: Gastroenterology 79:912-916, 1980.
3. Abernethy DR, Greenblatt DJ, Divoll M, et al: Psychopharmacology 80:275-278, 1983.
4. Abernethy DR, Greenblatt DJ, Divoll M, et al: N Engl J Med 306:791-792, 1982.
5. Ochs HR, Greenblatt DJ, Abernethy DR: Data on file, Wyeth Laboratories.

Wyeth Laboratories
Philadelphia, PA 19101
TM

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Ativan® for (lorazepam) Ⓒ Anxiety

See important information on following page.

Brief Summary of Prescribing Information.

Indications and Usage: Management of anxiety disorders or short-term relief of symptoms of anxiety or anxiety associated with depressive symptoms. Anxiety or tension associated with stress of everyday life usually does not require treatment with an anxiolytic.

Effectiveness in long-term use, i.e., more than 4 months, has not been assessed by systematic clinical studies. Reassess periodically usefulness of the drug for the individual patient.

Contraindications: Known sensitivity to benzodiazepines or acute narrow-angle glaucoma

Warnings: Not recommended in primary depressive disorders or psychoses. As with all CNS-acting drugs, warn patients not to operate machinery or motor vehicles, and of diminished tolerance for alcohol and other CNS depressants.

Physical and Psychological Dependence: Withdrawal symptoms like those noted with barbiturates and alcohol have occurred following abrupt discontinuance of benzodiazepines (including convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Addiction-prone individuals, e.g. drug addicts and alcoholics, should be under careful surveillance when on benzodiazepines because of their predisposition to habituation and dependence. Withdrawal symptoms have also been reported following abrupt discontinuance of benzodiazepines taken continuously at therapeutic levels for several months.

Precautions: In depression accompanying anxiety, consider possibility for suicide.

For elderly or debilitated patients, initial daily dosage should not exceed 2mg to avoid oversedation. Terminate dosage gradually since abrupt withdrawal of any antianxiety agent may result in symptoms like those being treated: anxiety, agitation, irritability, tension, insomnia and occasional convulsions. Observe usual precautions with impaired renal or hepatic function. Where gastrointestinal or cardiovascular disorders coexist with anxiety, note that lorazepam has not been shown of significant benefit in treating gastrointestinal or cardiovascular component. Esophageal dilation occurred in rats treated with lorazepam for more than 1 year at 6mg/kg/day. No effect dose was 1.25mg/kg/day (about 6 times maximum human therapeutic dose of 10mg/day). Effect was reversible only when treatment was withdrawn within 2 months of first observation. Clinical significance is unknown; but use of lorazepam for prolonged periods and in geriatrics requires caution and frequent monitoring for symptoms of upper G.I. disease. Safety and effectiveness in children under 12 years have not been established.

ESSENTIAL LABORATORY TESTS: Some patients have developed leukopenia; some have had elevations of LDH. As with other benzodiazepines, periodic blood counts and liver function tests are recommended during long-term therapy.

CLINICALLY SIGNIFICANT DRUG INTERACTIONS: Benzodiazepines produce CNS depressant effects when administered with such medications as barbiturates or alcohol.

CARCINOGENESIS AND MUTAGENESIS: No evidence of carcinogenic potential emerged in rats during an 18-month study. No studies regarding mutagenesis have been performed.

PREGNANCY: Reproductive studies were performed in mice, rats, and 2 strains of rabbits. Occasional anomalies (reduction of tarsals, tibia, metatarsals, malrotated limbs, gastroschisis, malformed skull and microphthalmia) were seen in drug-treated rabbits without relationship to dosage. Although all these anomalies were not present in the concurrent control group, they have been reported to occur randomly in historical controls. At 40mg/kg and higher, there was evidence of fetal resorption and increased fetal loss in rabbits which was not seen at lower doses. Clinical significance of these findings is not known. However, increased risk of congenital malformations associated with use of minor tranquilizers (chlordiazepoxide, diazepam and meprobamate) during first trimester of pregnancy has been suggested in several studies. Because use of these drugs is rarely a matter of urgency, use of lorazepam during this period should almost always be avoided. Possibility that a woman of child-bearing potential may be pregnant at institution of therapy should be considered. Advise patients if they become pregnant to communicate with their physician about desirability of discontinuing the drug. In humans, blood levels from umbilical cord blood indicate placental transfer of lorazepam and its glucuronide.

NURSING MOTHERS: It is not known if oral lorazepam is excreted in human milk like other benzodiazepines. As a general rule, nursing should not be undertaken while on a drug since many drugs are excreted in milk.

Adverse Reactions, if they occur, are usually observed at beginning of therapy and generally disappear on continued medication or on decreasing dose. In a sample of about 3,500 anxious patients, most frequent adverse reaction is sedation (15.9%), followed by dizziness (6.9%), weakness (4.2%) and unsteadiness (3.4%). Less frequent are disorientation, depression, nausea, change in appetite, headache, sleep disturbance, agitation, dermatological symptoms, eye function disturbance, various gastrointestinal symptoms and autonomic manifestations. Incidence of sedation and unsteadiness increased with age. Small decreases in blood pressure have been noted but are not clinically significant, probably being related to relief of anxiety.

Transient amnesia or memory impairment has been reported in association with the use of benzodiazepines.

Overdosage: In management of overdosage with any drug, bear in mind multiple agents may have been taken. Manifestations of overdosage include somnolence, confusion and coma. Induce vomiting and/or undertake gastric lavage followed by general supportive care, monitoring vital signs and close observation. Hypotension, though unlikely, usually may be controlled with Levarterenol Bitartrate Injection U.S.P. Usefulness of dialysis has not been determined.

Ativan® (IV) **for** (lorazepam) **Anxiety**

DOSAGE: Individualize for maximum beneficial effects. Increase dose gradually when needed, giving higher evening dose before increasing daytime doses. Anxiety, usually 2-3mg/day given b.i.d. or t.i.d.; dosage may vary from 1 to 10mg/day in divided doses. For elderly or debilitated, initially 1-2mg/day; insomnia due to anxiety or transient situational stress, 2-4mg h.s.

HOW SUPPLIED: 0.5, 1.0 and 2.0mg tablets.

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CONTINUING MEDICAL EDUCATION

(Continued from Page 23)

hrs. Fee: $295. Contact: IMEC, 64 Inverness Dr. East, Englewood, CO 80112.

April 20—**Cardiac Lecture Series: Advances in Research.** Heart Institute of the Desert at Annenberg Center, Rancho Mirage. Saturday. 2 hrs. Contact: Eisenhower Medical Center, 39000 Bob Hope Dr., Rancho Mirage 92270. (619) 568-2900.

April 26-28—**Coronary Artery Disease and Sudden Death: Primary and Secondary Prevention.** International Medical Education Corp. at Hyatt Union Square, San Francisco. Friday-Sunday. 13 hrs. Fee: $295. Contact: IMEC, 64 Inverness Dr. East, Englewood, CO 80112

April 26-28—**Vascular and Pulmonary Disease: Diagnosis and Management.** Medical Education Resources at Renaissance Hotel, San Francisco. Friday-Sunday. 13 hrs. Fee: $275. Contact: Leslie Shaffer, Medical Education Res., 5808 S. Rapp St., Ste 202, Littleton, CO 80120. (303) 798-9862.

EMERGENCY MEDICINE

January 19-26—**Management of Traumatic Emergencies.** UCSD at Kona Surf Resort, Kona, HI. Sunday-Sunday. 21 hrs. Fee: $315-$430. Contact: UCSD.

January 28-30—**Trauma: 1985.** UCSD at Vacation Village Resort, San Diego. Monday-Wednesday. 20 hrs.

February 4-8—**Topics in Emergency Medicine.** UCSF at Holiday Inn Union Square, San Francisco. Monday-Friday. 35 hrs. Fee: $425.

February 24-March 1—**Emergency Medicine: 1985.** UCD at Hyatt Lake Tahoe, Incline Village. Sunday-Sunday. Contact: UCD.

February 25-28—**Critical Care Medicine.** USC at MGM Grand Hotel, Las Vegas. Monday-Thursday. Contact: USC.

March 10-15—**6th Annual Mammoth Mountain Emergency Medicine Ski Conference.** UCI and Medical Conferences at Mammoth Lakes. Sunday-Friday. 20 hrs. Fee: $325. Contact: Med. Conf. Inc., PO Box 52-B, Newport Beach 92662. (714) 650-4156.

March 11-15—**Postgraduate Institute for Emergency Physicians, Symposium II.** UCSD at La Jolla Village Inn, La Jolla. Monday-Friday. 13-36 hrs. Fee: $200-675.

(Continued on Page 30)

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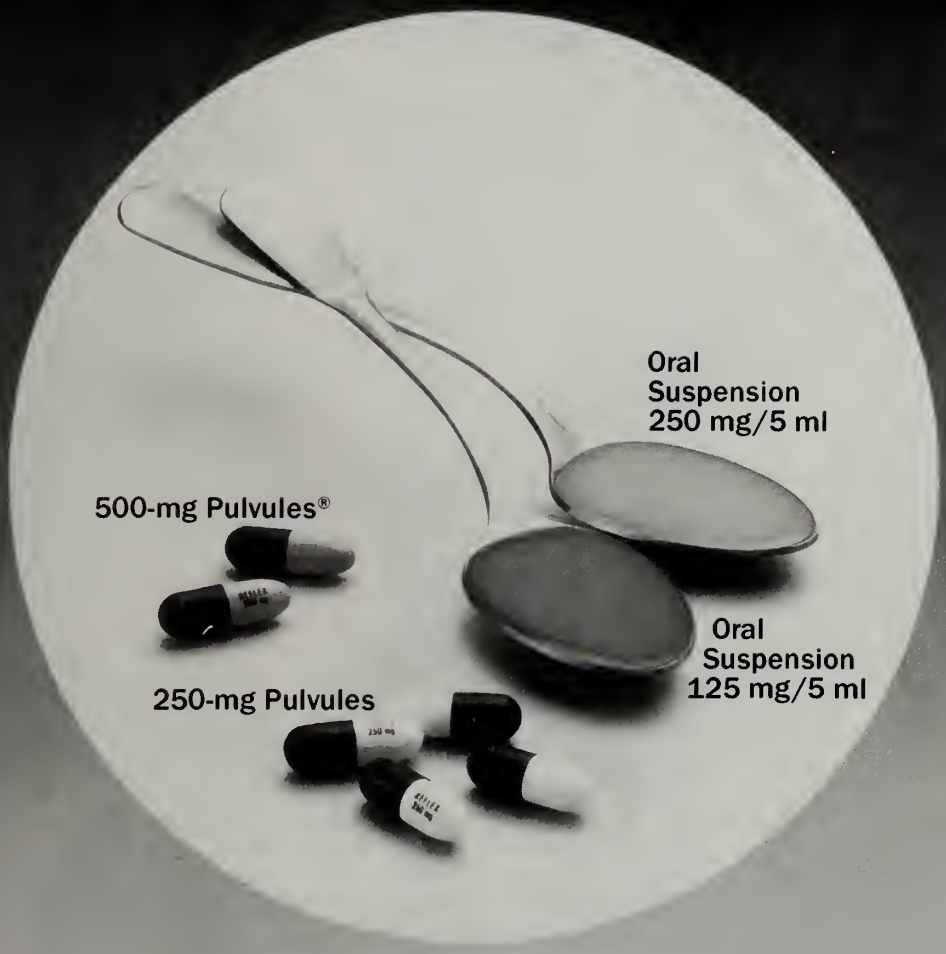

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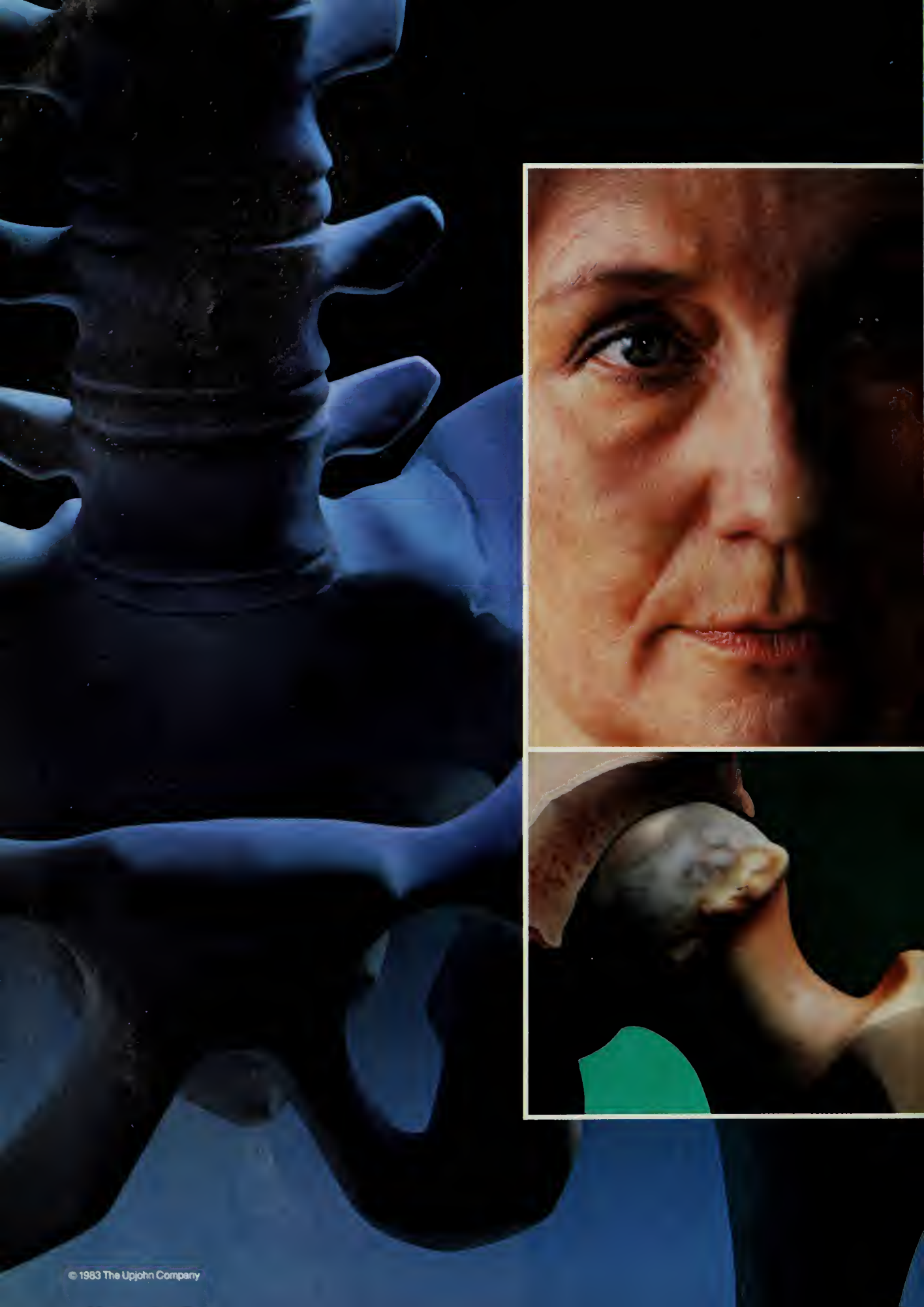

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The pain-relieving power of *Motrin* 600 mg tablets is welcome at any age. The advantages of *Motrin* become more important as patients grow older.

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Motrin is as effective as indomethacin in relieving arthritis pain and inflammation. *Motrin* causes significantly fewer CNS effects and about half as many GI complaints as indomethacin.

Motrin relieves pain as effectively as a combination of aspirin 650 mg plus codeine 60 mg, as documented in analgesia studies.

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Motrin® 600 mg TABLETS (ibuprofen)

One tablet t.i.d.

Please turn page for a brief summary of prescribing information.

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Motrin® Tablets (ibuprofen)

Contraindications: Anaphylactoid reactions have occurred in individuals hypersensitive to *Motrin* Tablets or with the syndrome of nasal polyps, angioedema and bronchospastic reactivity to aspirin, iodides, or other nonsteroidal anti-inflammatory agents.

Warnings: Peptic ulceration and GI bleeding, sometimes severe, have been reported. Ulceration, perforation and bleeding may end fatally. An association has not been established. Use *Motrin* Tablets under close supervision in patients with a history of upper gastrointestinal tract disease, after consulting ADVERSE REACTIONS. In patients with active peptic ulcer and active rheumatoid arthritis, try nonulcerogenic drugs, such as gold. If *Motrin* Tablets are used, observe the patient closely for signs of ulcer perforation or GI bleeding.

Chronic studies in rats and monkeys have shown mild renal toxicity with papillary edema and necrosis. Renal papillary necrosis has rarely been shown in humans treated with *Motrin* Tablets.

Precautions: Blurred and/or diminished vision, scotomata, and/or changes in color vision have been reported. If these develop, discontinue *Motrin* Tablets and the patient should have an ophthalmologic examination, including central visual fields and color vision testing.

Fluid retention and edema have been associated with *Motrin* Tablets; use with caution in patients with a history of cardiac decompensation or hypertension. In patients with renal impairment, reduced dosage may be necessary. Prospective studies of *Motrin* Tablets safety in patients with chronic renal failure have not been done.

Motrin Tablets can inhibit **platelet aggregation** and prolong bleeding time. Use with caution in persons with intrinsic coagulation defects and on anticoagulant therapy.

Patients should report signs or symptoms of **gastrointestinal ulceration** or bleeding, skin rash, weight gain, or edema.

Patients on prolonged **corticosteroid therapy** should have therapy tapered slowly when *Motrin* Tablets are added.

The antipyretic, anti-inflammatory activity of *Motrin* Tablets may mask inflammation and fever.

As with other nonsteroidal anti-inflammatory drugs, borderline elevations of liver tests may occur in up to 15% of patients. These abnormalities may progress, may remain essentially unchanged, or may be transient with continued therapy. Meaningful elevations of SGPT or SGOT (AST) occurred in controlled clinical trials in less than 1% of patients. Severe hepatic reactions, including jaundice and cases of fatal hepatitis, have been reported with ibuprofen as with other nonsteroidal anti-inflammatory drugs. If liver disease develops or if systemic manifestations occur (e.g. eosinophilia, rash, etc.), *Motrin* should be discontinued.

Drug interactions. *Aspirin:* used concomitantly may decrease *Motrin* blood levels.

Coumarin: bleeding has been reported in patients taking *Motrin* and coumarin.

Pregnancy and nursing mothers: *Motrin* should not be taken during pregnancy or by nursing mothers.

Adverse Reactions: The most frequent type of adverse reaction occurring with *Motrin* is gastrointestinal of which one or more occurred in 4% to 16% of the patients.

Incidence Greater than 1% (but less than 3%)—Probable Causal Relationship

Gastrointestinal: Nausea;* epigastric pain;* heartburn;* diarrhea, abdominal distress, nausea and vomiting, indigestion, constipation, abdominal cramps or pain, fullness of GI tract (bloating and flatulence); **Central Nervous System:** Dizziness;* headache, nervousness; **Dermatologic:** Rash* (including maculopapular type), pruritus; **Special Senses:** Tinnitus; **Metabolic/Endocrine:** Decreased appetite; **Cardiovascular:** Edema, fluid retention (generally responds promptly to drug discontinuation; see PRECAUTIONS).

Incidence less than 1%—Probable Causal Relationship**

Gastrointestinal: Gastric or duodenal ulcer with bleeding and/or perforation, gastrointestinal hemorrhage, melena, gastritis, hepatitis, jaundice, abnormal liver function tests; **Central Nervous System:** Depression, insomnia, confusion, emotional lability, somnolence, aseptic meningitis with fever and coma; **Dermatologic:** Vesiculobullous eruptions, urticaria, erythema multiforme, Stevens-Johnson syndrome, alopecia; **Special Senses:** Hearing loss, amblyopia (blurred and/or diminished vision, scotomata, and/or changes in color vision) (see PRECAUTIONS); **Hematologic:** Neutropenia, agranulocytosis, aplastic anemia, hemolytic anemia (sometimes Coombs positive), thrombocytopenia with or without purpura, eosinophilia, decreases in hemoglobin and hematocrit; **Cardiovascular:** Congestive heart failure in patients with marginal cardiac function, elevated blood pressure, palpitations; **Allergic:** Syndrome of abdominal pain, fever, chills, nausea and vomiting; anaphylaxis; bronchospasm (see CONTRAINDICATIONS); **Renal:** Acute renal failure in patients with pre-existing significantly impaired renal function, decreased creatinine clearance, polyuria, azotemia, cystitis, hematuria; **Miscellaneous:** Dry eyes and mouth, gingival ulcer, rhinitis.

Incidence less than 1%—Causal Relationship Unknown**

Gastrointestinal: Pancreatitis; **Central Nervous System:** Paresthesias, hallucinations, dream abnormalities, pseudotumor cerebri; **Dermatologic:** Toxic epidermal necrolysis, photoallergic skin reactions; **Special Senses:** Conjunctivitis, diplopia, optic neuritis; **Hematologic:** Bleeding episodes (e.g., epistaxis, menorrhagia); **Metabolic/Endocrine:** Gynecomastia, hypoglycemic reaction; **Cardiovascular:** Arrhythmias (sinus tachycardia, sinus bradycardia); **Allergic:** Serum sickness, lupus erythematosus syndrome, Henoch-Schönlein vasculitis; **Renal:** Renal papillary necrosis.

*Reactions occurring in 3% to 9% of patients treated with *Motrin*. (Those reactions occurring in less than 3% of the patients are unmarked.)

**Reactions are classified under *"Probable Causal Relationship (PCR)"* if there has been one positive rechallenge or if three or more cases occur which might be causally related. Reactions are classified under *"Causal Relationship Unknown"* if seven or more events have been reported but the criteria for PCR have not been met.

Overdosage: In cases of acute overdosage, the stomach should be emptied. The drug is acidic and excreted in the urine so alkaline diuresis may be beneficial.

Dosage and Administration: Rheumatoid arthritis and osteoarthritis. Suggested dosage is 300, 400, or 600 mg t.i.d. or q.i.d. Do not exceed 2400 mg per day. Mild to moderate pain: 400 mg every 4 to 6 hours as necessary.

Caution: Federal law prohibits dispensing without prescription.

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MED B-7-S

J-3253 June 1983

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CONTINUING MEDICAL EDUCATION

(Continued from Page 26)

April 6-13—**Emergency Medicine—1985.** USC at Royal Lahaina Hotel, Maui. One week. 26.5 hrs. Fee: $495.

April 24-26—**Clinical Advances and Research Updates in Emergency Medicine.** UCSF at Holiday Inn—Golden Gateway, San Francisco. Wednesday-Friday. 15 hrs. Fee: $300.

INTERNAL MEDICINE

January 24-26—**Nephrology for the Consultant.** UCSD at Sheraton Harbor Island West, San Diego. Thursday-Saturday. 18 hrs. Fee: $300. Contact: UCSD.

January 24-26—**Advanced Nephrology: Nephrology for the Consultant.** UCSD at Sheraton Harbor Island West, San Diego. Thursday-Saturday. 18 hrs. Contact: UCSD.

February 8-9—**Infectious Disease: Clinical Update.** UCD at Red Lion Motor Inn, Sacramento. Friday-Saturday. Contact: UCD.

February 12-17—**18th Annual Recent Advances in Neurology.** UCSF at Fairmont Hotel, San Francisco. Tuesday-Sunday. Contact: UCSF.

February 13-14—**Rheumatology Subspecialty Course.** UCSD at Town and Country Hotel, San Diego. Wednesday-Thursday. 12 hrs.

February 15-19—**10th Annual Postgraduate Topics in Internal Medicine.** UCSD at Town and Country Hotel, San Diego. Wednesday-Tuesday. 36 hrs.

February 17-22—**Advanced Problems in Infectious Diseases and Toxicology.** UCSD at Continental Inn, Aspen. Sunday-Friday. 21 hrs. Fee: $315-$430. Contact: UCSD.

February 21-24—**Federation of Societies of Neurological Science** at Hotel Intercontinental, San Diego. Thursday-Friday. 18 hrs. Contact: James Grisolia, MD, 4020 5th Ave., Ste. 404, San Diego 92138. (619) 297-1155.

February 27-March 2—**Gastroenterology Subspecialty Course.** UCSD at Town and Country Hotel, San Diego. Wednesday-Saturday. 12 hrs.

March 8-10—**Frontiers of Rheumatology.** Annenberg Center for Health Science, Rancho Mirage. Friday-Sunday. Contact: Eisenhower Medical Center, 39000 Bob Hope Dr., Rancho Mirage, CA 92270.

March 13-16—**Office Endocrinology: 1985.** UCSF at Granlibakken Ski and Raquet Resort, Tahoe City. Wednesday-Saturday.

March 18-20—**Gastroenterology Course.** UCSF at Yosemite. Monday-Wednesday. Contact: UCSF.

March 19-22—**Internal Medicine Update.** UCD at Red Lion Motor Inn, Sacramento. Tuesday-Friday.

April 22-24—**Advances in Infectious Diseases.** UCSF at Mark Hopkins Hotel, San Francisco. Monday-Wednesday. Fee: $325.

April 27—**Nephrology.** UCSF at Fresno. Saturday.

OBSTETRICS AND GYNECOLOGY

February 3-7—**OB/GYN Update: 1985.** UCD at Hyatt Lake Tahoe, Incline Village. Sunday-Thursday. Contact: UCD.

February 9-10—**Los Angeles OB/GYN Forum.** Los Angeles OB/GYN Society at Beverly Hilton Hotel, Beverly Hills. Saturday-Sunday. 10 hrs. Fee: $80. Contact: Director of Medical Education, LA OB/GYN Society, 5820 Wilshire Blvd, #500, Los Angeles, CA 90036. (213) 937-5514.

February 9-16—**13th Obstetric Anesthesia Conference.** Ohio State University at Sheraton Waikiki Hotel, Waikiki, HI. One week. 20 hrs. Contact: Arlene Rogers, OSUH, Department of Anesthesiology, 410 W. 10th Ave., Columbus, OH 43210. (614) 421-8487.

February 11-15—**San Diego Abdominal and Obstetrical Imaging Symposium Update.** UCSD at Hotel Intercontinental, San Diego. Fee: $425. Contact: UCSD.

February 11-15—**40th Annual Postgraduate Assembly.** Ob/Gyn Assembly of So. California at Beverly Hilton Hotel, Beverly Hills. Monday-Friday. 28 hrs. Contact: Ob/Gyn Assembly, 5820 Wilshire Blvd #500, Los Angeles 90036. (213) 937-5514.

February 16-23—**Perinatal Medicine.** USC at Royal Lahaina, Maui, HI. One week.

February 23—**OB/GYN.** UCSF at Fresno. Saturday. Contact: UCSF.

March 2-9—**6th Annual Symposium on Current Topics in Obstetrics.** UCI at Aspen, Colorado. One week. 23 hrs. Contact: UCI.

March 7-10—**Recent Advances in OB/GYN: 8th Annual.** UCSD at Hotel Intercontinental, San Diego. Thursday-Saturday. 21 hrs.

March 15-16—**30th Annual T. Hart Baker, MD Symposium.** Southern California Kaiser Permanente at Hyatt Regency Hotel, Long Beach. Friday-Saturday. Contact: Southern California Kaiser Permanente, 4747 Sunset Blvd, Los Angeles 90027.

March 16-17—**Uses of Real-time Ultrasound in Gynecology and Infertility.** UCI at Hotel Inter-Continental, San Diego. Saturday-Sunday. 16 hrs.

March 21-24—**Changing Practice of Obstetrical Anesthesiology and High Risk Pregnancy.** UCSF at Hotel Meridien, San Francisco. Thursday-Sunday. 16 hrs.

March 22-24—**Gynecology Surgery with Emphasis on Gynecologic Urology.** UCI at The Palm Springs Marquis, Palm Springs. Friday-Sunday. 15 hrs.

OPHTHALMOLOGY

January 24-25—**YAG Laser Source.** UCSD at UCSD Medical Center. Thursday-Friday. 12 hrs. Contact: UCSD.

January 25-26—**Fluorescein Angiography Techniques and Interpretation.** JSEI at Los Angeles. Friday-Saturday. 16 hrs. Fee: $250. Contact: Lu Hendricks, Academic Program Dir., Jules Stein Eye Institute, 800 Westwood Plaza, Los Angeles 90024. (213) 825-4617.

February 8-10—**5th Annual Current Concepts in Ophthalmology 1985.** UCSD at Hotel Del Coronado, San Diego. Friday-Saturday. 15 hrs. Contact: UCSD.

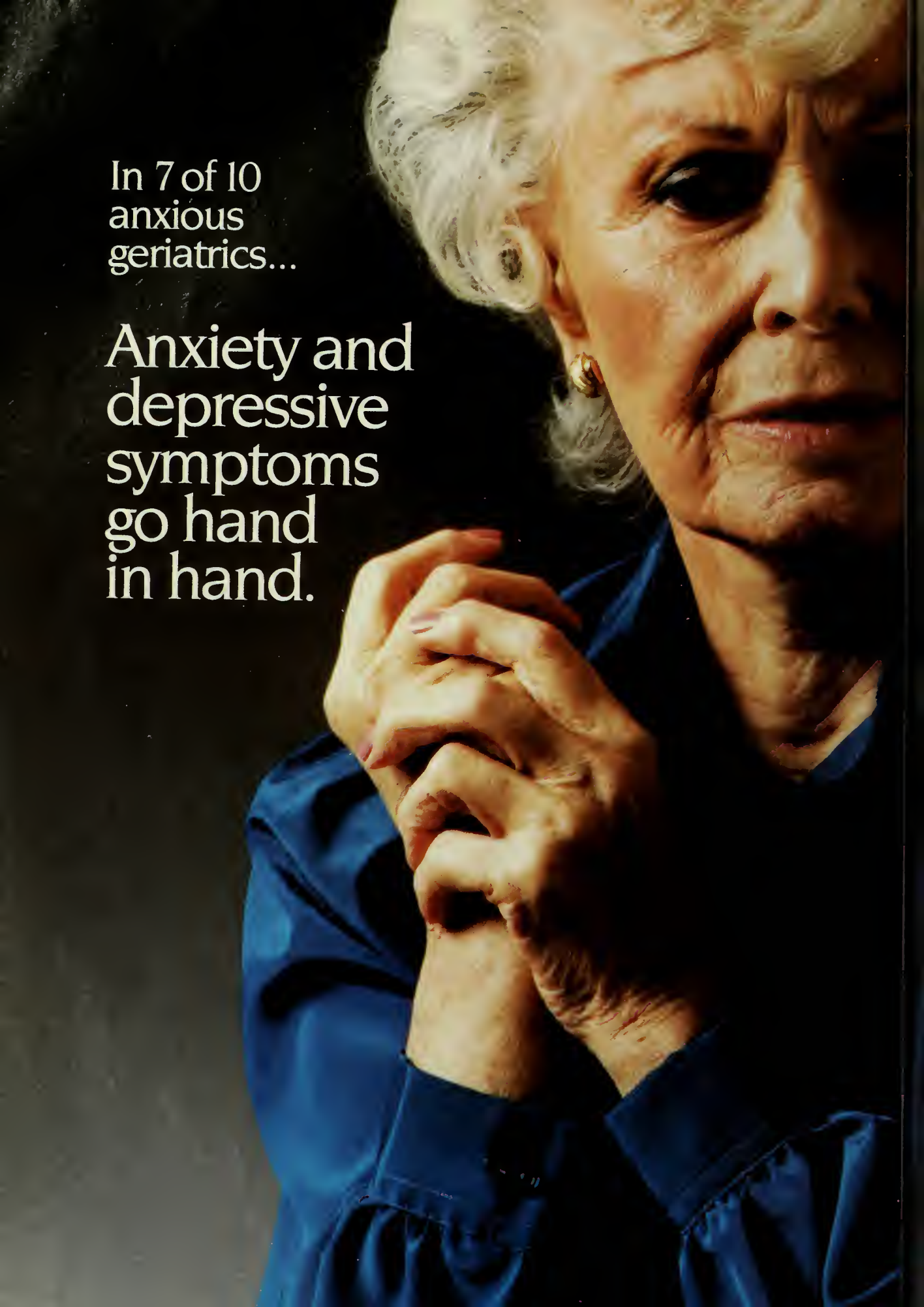
March 1-2—**14th Jules Stein Seminar: Retino Vitreal.** Jules Stein Eye Institute at Century Plaza Hotel, Los Angeles. 16 hrs. Contact: JSEI, UCLA School of Medicine, Los Angeles 90024. (213) 825-4617.

March 9—**Ophthalmology Residents and Fellows Day.** JSFI at Los Angeles. Saturday. 5 hrs. Fee: $15 Non-members. Contact: Lu Hendricks, JSEI, 800 Westwood Plaza, Los Angeles 90024. (213) 825-4617.

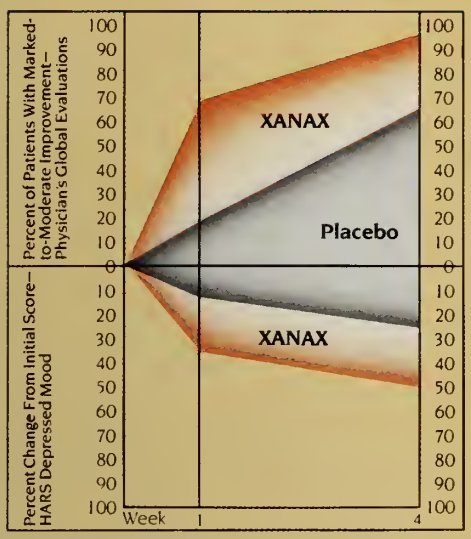
March 14-15—**Modern Surgical Techniques and Their Effects of the Cornea.** Pacific Medical Center at Clift Hotel, San Francisco. Thursday-Friday. Contact: Pacific Medical Center, Continuing Education, PO Box 7999, San Francisco 94120. (415) 563-4321, ext. 2761.

April 12-13—**16th Jules Stein Lecture and Annual Postgraduate Seminar.** JSEI. Saturday-Sunday. 16 hrs. Fee: $375. Contact: Lu Hendricks, Jules Stein Eye Institute, 800 Westwood Plaza, Los Angeles 90024. (213) 825-4617.

(Continued on Page 34)


In 7 of 10
anxious
geriatrics...
Anxiety and
depressive
symptoms
go hand
in hand.

Xanax rapidly relieves anxiety with depressive symptoms.



In a recent clinical study[1] of 83 geriatric patients with clinical anxiety, 73% were diagnosed as having symptoms of depressed mood.

XANAX is well suited for therapy because it demonstrates greater efficacy than placebo in reducing the Hamilton Anxiety Rating Scale Total Score and individual items including depressed mood (see Figure).

With clinical advantages for geriatric patients.

- **Rapidly relieves** the symptoms of anxiety
- **Rapidly relieves** associated depressed mood
- **Well tolerated**—mild, transient drowsiness, the most commonly reported side effect the first week of therapy, shows a marked decrease thereafter and is not significantly different from that of placebo
- **Does not cause** cardiotoxicity
- **Specific geriatric dosage**—0.25 mg, two or three times daily

1 Cohn JB. Double-blind safety and efficacy comparison of alprazolam and placebo in the treatment of anxiety in geriatric patients. *Curr Ther Res* 1984;35(1):100-112

Xanax® 0.25 mg Tablets
alprazolam C IV

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Upjohn THE UPJOHN COMPANY
Kalamazoo, Michigan 49001 USA

Please see next page for brief summary of prescribing information.

XANAX® Tablets
(alprazolam) ©

CONTRAINDICATIONS
Patients with sensitivity to this drug or other benzodiazepines and in acute narrow angle glaucoma

WARNINGS
Not of value in psychotic patients Caution patients against hazardous occupations requiring complete mental alertness and about the simultaneous ingestion of alcohol and other CNS depressant drugs

Benzodiazepines can cause fetal harm in pregnant women. Warn patients of the potential hazard to the fetus Avoid during the first trimester.

PRECAUTIONS
General: The dosage of XANAX Tablets should be reduced or withdrawn gradually, since withdrawal seizures have been reported upon abrupt withdrawal. If XANAX is combined with other psychotropics or anticonvulsant drugs, consider drug potentiation (See Drug Interaction section.) Exercise the usual precautions regarding size of the prescription for depressed or suicidal patients. In elderly and debilitated patients, use the lowest possible dosage. (See Dosage and Administration.) Observe the usual precautions in treating patients with impaired renal or hepatic function.

Information for Patients: Alert patients about (a) consumption of alcohol and drugs, (b) possible fetal abnormalities, (c) operating machinery or driving, (d) not increasing dose of the drug due to risk of dependence, (e) not stopping the drug abruptly *Laboratory Tests:* Not ordinarily required in otherwise healthy patients *Drug Interactions:* Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistamines, ethanol and other CNS depressants. Pharmacokinetic interactions with benzodiazepines have been reported *Drug/Laboratory Test Interactions:* No consistent pattern for a specific drug or specific test *Carcinogenesis, Mutagenesis, Impairment of Fertility:* No carcinogenic potential or impairment of fertility in rats. *Pregnancy.* See Warnings. *Nonteratogenic Effects:* The child born of a mother on benzodiazepines may be at some risk for withdrawal symptoms and neonatal flaccidity. *Labor and Delivery:* No established use. *Nursing Mothers:* Benzodiazepines are excreted in human milk Women on XANAX should not nurse. *Pediatric Use:* Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS
Side effects are generally observed at the beginning of therapy and usually disappear with continued medication In the usual patient, the most frequent side effects are likely to be an extension of the pharmacological activity of XANAX, e.g., drowsiness or lightheadedness

Central nervous system. Drowsiness, lightheadedness, depression, headache, confusion, insomnia, nervousness, syncope, dizziness, akathisia, and tiredness/sleepiness.

Gastrointestinal: Dry mouth, constipation, diarrhea, nausea/vomiting, and increased salivation.

Cardiovascular Tachycardia/palpitations, and hypotension.

Sensory Blurred vision

Musculoskeletal: Rigidity and tremor.

Cutaneous: Dermatitis/allergy

Other side effects: Nasal congestion, weight gain, and weight loss.

In addition, the following adverse events have been reported with the use of anxiolytic benzodiazepines, dystonia, irritability, concentration difficulties, anorexia, loss of coordination, fatigue, sedation, slurred speech, jaundice, musculoskeletal weakness, pruritus, diplopia, dysarthria, changes in libido, menstrual irregularities, incontinence and urinary retention.

Paradoxical reactions such as stimulation, agitation, increased muscle spasticity, sleep disturbances, and hallucinations may occur. Should these occur, discontinue the drug.

During prolonged treatment, periodic blood counts, urinalysis, and blood chemistry analysis are advisable. Minor EEG changes, of unknown significance, have been observed

DRUG ABUSE AND DEPENDENCE
Physical and Psychological Dependence: Withdrawal symptoms have occurred following abrupt discontinuance of benzodiazepines. Withdrawal seizures have occurred upon rapid decrease or abrupt discontinuation of therapy. In all patients, dosage should be gradually tapered under close supervision. Patients with a history of seizures or epilepsy should not be abruptly withdrawn from XANAX Addiction-prone individuals should be under careful surveillance. *Controlled Substance Class:* XANAX is a controlled substance and has been assigned to schedule IV

DOSAGE AND ADMINISTRATION
The usual starting dose is 0.25 to 0.5 mg, t.i.d Maximum total daily dose is 4 mg In the elderly or debilitated, the usual starting dose is 0.25 mg, two or three times daily Reduce dosage gradually when terminating therapy, by no more than one milligram every three days

CAUTION: FEDERAL LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION B-3-S

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CONTINUING MEDICAL EDUCATION

(Continued from Page 31)

PATHOLOGY

February 3-6—**12th Annual Course in Genitourinary Pathology.** UCI at Memorial Medical Center, Long Beach. Sunday-Wednesday. 36 hrs. Contact: UCI.

February 16—**Oxygen Radicals, Pathology and Aging.** UCSD at Holiday Inn at the Embarcadero, San Diego. Saturday.

PEDIATRICS

January 25-26—**Advanced Fetal Heart Rate Monitoring Seminar.** UCI at South Coast Plaza Hotel, Costa Mesa. Friday-Sunday. 12 hrs. Contact; UCI.

January 25-27—**23rd Annual Clinical Conference in Pediatric Anesthesiology.** See Anesthesiology, January 25-27.

February 2-9—**Pediatric Emergencies.** UCSD at Snowbird Resort, Utah. One week. 21 hrs. Fee: $315-$350. Contact: UCSD.

March 7-9—**Brain Insults in Infants and Children: Pathology, Evaluation, Diagnosis and Acute Management.** UCSD at Holiday Inn Embarcadero, San Diego. 17 hrs. Contact: UCSD.

March 14-15—**Combined Southern California Pediatric Postgraduate Meeting.** American Association of Pediatricians at Palm Springs. Thursday-Friday. Contact: AAP at (213) 757-1198.

April 10—**Pediatrics: Infections in Infants and Children.** LLU. Wednesday. 4 hrs.

April 17-19—**10th Annual Symposium "Care of the Sick Newborn."** UCI at Hyatt Regency Hotel, Long Beach. Wednesday-Friday. 17 hrs.

April 19-20—**Annual Pediatric Program.** UCD at Sacramento Inn, Sacramento. Friday-Sunday.

PSYCHIATRY

January 27-February 1—**Midwinter Program for Psychiatrists.** UCD at Hyatt Lake Tahoe, Incline Village. Sunday-Friday. Contact: UCD.

March 29-31—**General Psychiatry Board Review.** UCSF at Golden Gateway Holiday Inn, San Francisco. Friday-Sunday.

April 27-28—**The Cutting Edge 1985—Clinical Applications of Kohut's Theories on Narcissism.** UCSD. Saturday-Sunday. 12.5 hrs.

RADIOLOGY

February 27-March 1—**5th Annual Approaches: Radiologic, Oncology, Biology and Physics.** UCSF at Fairmont Hotel, San Francisco. Wednesday-Friday. Contact: UCSF.

March 6-9—**6th Annual Sierra Radiology Conference.** Sacramento Radiology Society at Hyatt Lake Tahoe, Incline Village. Wednesday-Saturday. 20 hrs. Contact: John P. Walter, MD, Program Director, Sacramento Radiology Research and Education Found., PO Box 19184, Sacramento 95819.

March 11-15—**28th Annual Postgraduate Course in Diagnostic Radiology.** UCSF at Fairmont Hotel, San Francisco. Monday. 33 hrs.

March 18-23—**Diagnostic Imaging 1985.** UCSF at Waiohai Hotel, Kauai. Monday-Saturday. 26 hrs. Fee: $425.

April 14-19—**Adult and Pediatric Radiology for Emergency Physicians.** UCSD at Waiohai Hotel, Kauai. Sunday-Friday. 21 hrs. Fee: $315-430.

April 29-May 3—**5th Annual Residents Radiology Review Course.** UCSD at Town and Country Inn, San Diego. Monday-Friday.

SPORTS MEDICINE

January 26—**Nutrition for Athletic Performance.** American Heart Association at University of California at Berkeley, Berkeley. Saturday. 4 hrs. Fee: $40. Contact: American Heart Association, PO Box 5157, Oakland 94605. (415) 632-9606.

February 9-16—**Sports Now V.** American College of Sports Medicine at Maui Surf Hotel, Maui. One week. 20 hrs. Contact: Stuart Zeman, Course Chairman, 2999 Regent St., Berkeley 94705. (415) 540-8686.

March 18-22—**University of Hawaii Sports Medicine Course.** Ohio State University at Princess Kaiulani Hotel, Waikiki, HI. Monday-Friday. 18 hrs. Fee: $280. Contact: Ms. Joy Lewis, Box CEW-CCECS, 2530 Dole St., Honolulu, HI 96822. (808) 948-8244.

SURGERY

January 18-19—**Surgical Superbowl.** Santa Clara County Surgical Society at Hyatt San Jose. Friday-Saturday. 16 hrs. Contact: Richard Hardy, MD, 2505 Samaritan Dr. #302, San Jose 95124.

January 18-19—**7th Annual Postgraduate Course in Surgery.** UCD at Capitol Plaza Holiday Inn, Sacramento. Friday-Saturday. Contact: UCD.

January 21-25—**8th Annual San Diego Postgraduate Assembly in Surgery.** UCSD. Monday-Friday. Contact: UCSD.

February 9-10—**The 23rd Annual Surgery Symposium.** Southern California Permanente Group at Casa Sirena Marina Hotel, Oxnard. Saturday-Sunday. Contact: Southern California Kaiser Permanente Group, 4747 Sunset Blvd, Los Angeles 90027.

February 11-15—**Basic Microsurgery Training Workshop.** UCSD. Monday-Friday. 34 hrs. Fee: $1,200. Contact: UCSD.

March 4-8—**Surgical Forum.** Society of Graduate Surgeons of Los Angeles County at Ambassador Hotel, Los Angeles. Monday-Friday. 31 hrs. Fee: $400. Contact: Director of Medical Education, Society of Graduate Surgeons, 5820 Wilshire Blvd., #500, Los Angeles 90036.

Marach 8-10—**Surgery for Sleep Apnea Snoring—Current Advances.** UCI at Marriott Hotel, Newport Beach. Friday-Sunday. 11 hrs.

March 18-22—**Basic Microsurgery Training Workshop.** UCSD. Monday-Friday. 34 hrs. Fee: $1,200. Contact: UCSD.

March 25-29—**Advanced Microsurgery Training Workshop.** UCSD. Monday-Friday. 34 hrs. Fee: $1,200. Contact: UCSD.

April 1-5—**Basic Microsurgery Training Workshop.** UCSD. Monday-Friday. 34 hrs. Fee: $1,200.

April 1-5—**12th Annual Spring Meeting of American College of Surgeons** at Hilton Hawaiian Village Hotel, and Westin Ilikai Hotel, Hawaii. Sunday-Thursday. Contact: ACS, 55 E. Erie St., Chicago, Il 60611.

April 24-26—**Postgraduate Course in General Surgery.** UCSF at Hilton Hotel, San Francisco. Wednesday-Thursday.

OF INTEREST TO ALL PHYSICIANS

January 17-19—**Physician & Hospital Conference.** USC at Hyatt Del Monte, Monterey. Thursday-Friday.

January 20-23—**54th Annual Midwinter Clinical Conference.** Research Study Club of Los Angeles at

(Continued on Page 124)

New Hydrochlorothiazide Dosage Guidelines from High BP Joint National Committee

START WITH

25 mg.

The 1984 Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure recommends starting with the smallest effective dose in diuretic therapy. For hydrochlorothiazide the initial dosage recommended is 25 mg.

DYAZIDE® contains the dosage of hydrochlorothiazide recommended by JNC III.

DYAZIDE® also contains 50 mg. of triamterene—the initial dosage of that agent recommended by JNC III.

In Hypertension*...When you want the safety and efficacy of low dosage thiazide therapy plus potassium conservation

P R E S C R I B E

DYAZIDE®

Each capsule contains 50 mg. of Dyrenium® (brand of triamterene) and 25 mg. of hydrochlorothiazide.

Serum K^+ and BUN should be checked periodically (see Warnings and Precautions).

Before prescribing, see complete prescribing information in SK&F CO. literature or *PDR*. The following is a brief summary.

WARNING
This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Contraindications: Concomitant use with other potassium-sparing agents such as spironolactone or amiloride. Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics.

Precautions: Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids, and during concurrent use with amphotericin B or corticosteroids or corticotropin [ACTH]). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Cumulative effects of the drug may develop in patients with impaired renal function. Thiazides should be used with caution in patients with impaired hepatic function. They can precipitate coma in patients with severe liver disease. Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic and hemolytic anemia have been reported with thiazides. Thiazides may cause manifestation of latent diabetes mellitus. The effects of oral anticoagulants may be decreased when used concurrently with hydrochlorothiazide; dosage adjustments may be necessary. Clinically insignificant reductions in arterial responsiveness to norepinephrine have been reported. Thiazides have also been shown to increase the paralyzing effect of nondepolarizing muscle relaxants such as tubocurarine. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. Triamterene has been found in renal stones in association with the other usual calculus components. Therefore, 'Dyazide' should be used with caution in patients with histories of stone formation. A few occurrences of acute renal failure have been reported in patients on 'Dyazide' when treated with indomethacin. Therefore, caution is advised in administering nonsteroidal anti-inflammatory agents with 'Dyazide'. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine. Hypokalemia is uncommon with 'Dyazide', but should it develop, corrective measures should be taken such as potassium supplementation or increased dietary intake of potassium-rich foods. Corrective measures should be instituted cautiously and serum potassium levels determined. Discontinue corrective measures and 'Dyazide' should laboratory values reveal elevated serum potassium. Chloride deficit may occur as well as dilutional hyponatremia. Concurrent use with chlorpropamide may increase the risk of severe hyponatremia. Serum PBI levels may decrease without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. 'Dyazide' should be withdrawn before conducting tests for parathyroid function.

Thiazides may add to or potentiate the action of other antihypertensive drugs.

Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances; postural hypotension (may be aggravated by alcohol, barbiturates, or narcotics). Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and respiratory distress including pneumonitis and pulmonary edema, transient blurred vision, sialadenitis, and vertigo have occurred with thiazides alone. Triamterene has been found in renal stones in association with other usual calculus components. Rare incidents of acute interstitial nephritis have been reported. Impotence has been reported in a few patients on 'Dyazide', although a causal relationship has not been established.

Supplied: 'Dyazide' is supplied as a maroon and white capsule, in bottles of 1000 capsules; Single Unit Packages (unit-dose) of 100 (intended for institutional use only); in Patient-Pak™ unit-of-use bottles of 100.

BRS-DZ:L36

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The unique red and white Dyazide® capsule: Your assurance of SK&F quality.

Clinical Investigation

Quadruple Injection of Hypothalamic Peptides to Evaluate Pituitary Function in Normal Subjects

K. C. KALTENBORN, MD, *and* WILLIAM JUBIZ, MD, *Salt Lake City*

A single intravenous injection of four hypothalamic releasing hormones—corticotropin-, growth hormone-, gonadotropin- and thyrotropin-releasing hormones—was administered to normal subjects. Except for the plasma adrenocorticotropic hormone (ACTH) level, a statistically significant increase in all anterior pituitary hormone levels occurred. Transient flushing was the only consistent side effect. In the same persons, results were compared with those obtained with insulin-induced hypoglycemia and a single-dose overnight metyrapone test. Growth hormone and cortisol responses to insulin-induced hypoglycemia were similar but prolactin increment was less than that obtained by the peptide injection. ACTH increments from both tests were substantially less than those obtained by the overnight metyrapone test.

We conclude that pituitary function can be effectively studied in normal subjects by the combination of a metyrapone test with a triple bolus of growth hormone-, thyrotropin- and gonadotropin-releasing hormones, but not by a quadruple bolus of the hypothalamic peptides. Compared with insulin-induced hypoglycemia, this approach yields more information with fewer side effects.

(Kaltenborn KC, Jubiz W: Quadruple injection of hypothalamic peptides to evaluate pituitary function in normal subjects [Clinical Investigation]. West Med 1985 Jan; 142:37-41)

In recent years two new hypothalamic peptides, corticotropin-releasing hormone (CRH) and growth hormone-releasing hormone (GRH), have been identified and are now available for research and possible clinical application.[1,2] Ovine CRH is a 41-amino-acid peptide that stimulates adrenocorticotropic hormone (ACTH) release and has recently been used to evaluate cases of Cushing's disease.[3] GRH is a 44-amino-acid peptide extracted from a human pancreatic tumor that raises the plasma growth hormone level and has been used in humans to study acromegaly, hypopituitarism and growth hormone:age relationships.[4,5] Two other hypothalamic peptides have been available for some years and are well established for use in clinical testing. These are thyrotropin-releasing hormone (TRH) and gonadotropin-releasing hormone (GnRH).[6-8] Thus, peptides are now available to stimulate selectively all of the known pituitary hormones.

Heretofore, provocative pituitary testing has involved a variety of methods, none of which is able to evaluate panpituitary secretory function without combining insulin-induced hypoglycemia. The aim of this study was to evaluate the anterior pituitary hormone response of normal persons to the simultaneous injection of TRH, GnRH, GRH and CRH and to compare this with the response obtained from the standard metyrapone and insulin-induced hypoglycemia tests.

Subjects and Methods

Subjects

Ten healthy male subjects aged 25 to 32 years (mean 28.6) and five healthy female subjects aged 30 to 59 years (mean 40.6) participated in the study. In the women, the quadruple bolus injection was administered within five days of onset of the menses. Informed consent was obtained from all participants. The study was approved by the Human Rights Committee at the University of Utah and the Food and Drug Administration.

Quadruple Bolus and Insulin Tests

The subjects were weighed and then kept at rest in the Clinical Research Center after an overnight fast. An intrave-

From the Division of Endocrinology and Metabolism, Department of Internal Medicine, Veterans Administration Medical Center and the University of Utah School of Medicine, Salt Lake City.

Dr Jubiz's research was supported by the Medical Research Service of the Veterans Administration and the Clinical Research Center, University of Utah School of Medicine.

Submitted, revised, September 9, 1984.

Reprint requests to K. C. Kaltenborn, MD, Division of Endocrinology and Metabolism (111E), VA Medical Center, 500 Foothill Blvd, Salt Lake City, UT 84148.

ABBREVIATIONS USED IN TEXT

ACTH = adrenocorticotropic hormone
CRH = corticotropin-releasing hormone
FSH = follicle-stimulating hormone
GnRH = gonadotropin-releasing hormone
GRH = growth hormone-releasing hormone
LH = luteinizing hormone
TRH = thyrotropin-releasing hormone
TSH = thyrotropin [thyroid-stimulating hormone]

nous cannula was inserted in a forearm 5 to 14 minutes before injection between 6:30 AM and 8 AM. A basal (20 ml) blood specimen was taken before each test. The hypothalamic peptides were prepared before injection in the following manner: GRH and CRH were dissolved in a solution of normal saline with 1 mmol of hydrochloric acid to increase solubility, 0.25% human albumin to minimize adsorption to the vial, syringe and tubing and 1% ascorbic acid to prevent oxidation. GnRH was dissolved in a diluent provided by Ayerst Laboratories. These solutions were mixed with TRH and diluted with normal saline to prepare 5-ml individualized aliquots containing the following: TRH, 3 μg per kg of body weight; GnRH, 2 μg per kg; CRH, 1.5 μg per kg, and GRH, 1.5 μg per kg. (These doses are similar to those used by previous investigators.[9-11]) Blood pressure and pulse were obtained at baseline and before each blood specimen was drawn. The material was injected over one minute and the subjects were monitored for symptoms of flushing or nausea. Specimens (15 ml of blood) were drawn through the catheter at 15, 30, 45, 60, 90 and 120 minutes and analyzed for cortisol, ACTH, luteinizing hormone (LH), follicle stimulating hormone (FSH), thyrotropin (TSH [thyroid-stimulating hormone]), growth hormone and prolactin levels. (The specimen for ACTH was drawn into a siliconized tube with ethylenediaminetetraacetic acid and immediately placed on ice.) At baseline and 120 minutes, a complete blood count, 20-channel chemistry panel and analysis of urine were also done. The 20-channel chemistry included sodium, potassium, chloride, carbon dioxide, glucose, blood urea nitrogen, creatinine, cholesterol, calcium, albumin, phosphorus, uric acid, bilirubin, alkaline phosphatase, lactic dehydrogenase, serum aspartate and serum alanine aminotransferases and γ-glutamyl transferase.

In the insulin hypoglycemia study, the subjects were injected with 0.1 unit of regular insulin per kilogram of body weight. Blood specimens (15 ml) were obtained at 15, 30, 45 and 60 minutes and analyzed for cortisol, ACTH, growth hormone, prolactin and glucose levels.

Metyrapone Test

Blood specimens for baseline 8 AM fasting cortisol and ACTH determinations were taken from each subject and they were then given 3 grams of metyrapone at midnight with a snack. The subject then fasted until 8 AM the following morning when specimens for ACTH, cortisol and plasma 11-deoxycortisol levels were obtained. There was an interval of at least five days between the metyrapone test and the other tests.

Hypothalamic Peptides

Synthetic TRH (protirelin [Relefact-TRH]) was obtained from Hoechst-Roussel Pharmaceuticals, Inc, and GnRH (gonadorelin hydrochloride [Factrel]) from Ayerst Laboratories. Synthetic ovine CRH and human pancreatic GRH were both obtained from Peninsula Laboratories (611 Taylor Way, Belmont, CA 94002). The 41-amino-acid CRH was confirmed for bioactivity by measuring ACTH release from cultured rat pituitary cells. The CRH and GRH were passed through millipore filtration and subsequent testing showed no bacterial contamination or pyrogens.

Statistical Analysis

Data were analyzed for statistical significance by Student's *t* test.

Hormone Assays

All hormones were measured in unextracted plasma (ACTH) or serum (other hormones) by commercially available radioimmunoassays. The following kits were used: Diagnostic Products Corporation for cortisol, Amerlex for FSH and LH, Immunonuclear for ACTH and growth-hormone, Hybritech Inc for prolactin, Micromedic Systems Inc for TSH and Radioassay Systems Laboratories for 11-deoxycortisol. All polypeptide radioimmunoassays have been tested for cross-reactivity against structurally similar peptides and were found to be less than 0.8% with the exception of the LH

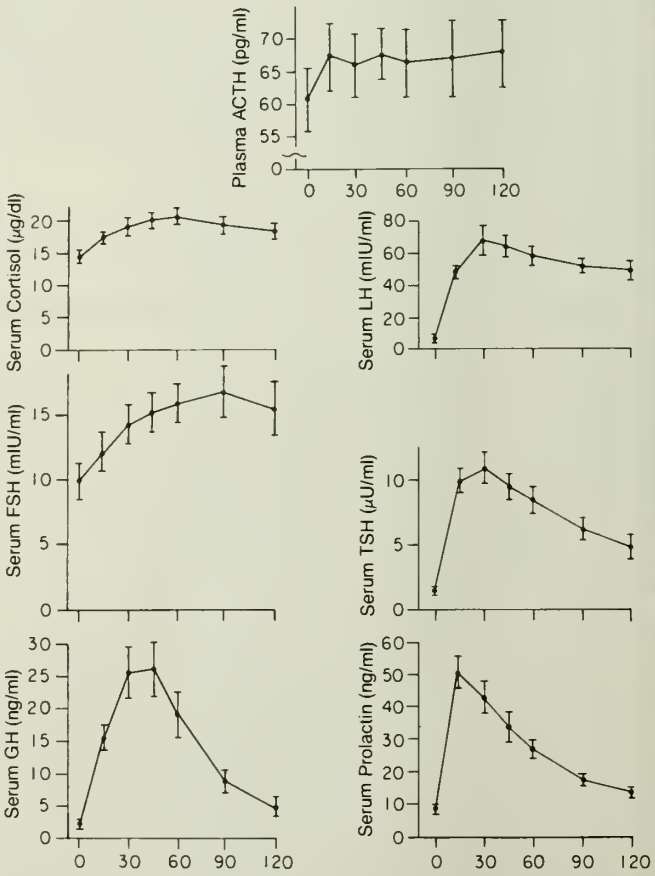

Figure 1—Plasma or serum hormone concentrations (mean ± SEM) in 15 normal subjects (10 men and 5 women) following the intravenous injection of corticotropin-releasing hormone, growth hormone-releasing hormone, gonadotropin-releasing hormone and thyrotropin-releasing hormone as a single bolus. All values for all hormones except for adrenocorticotropic hormone (ACTH) are statistically significant ($P < .05$) when compared with baseline. None of the values are significant for ACTH. LH = luteinizing hormone, FSH = follicle-stimulating hormone, TSH = thyrotropin, GH = growth hormone.

assay, which gave a 2.4% and 3.8% cross-reactivity to FSH and TSH, respectively. The cortisol assay had less than 1.5% cross-reactivity to other circulating steroids.

Results

Hormone measurements in response to the quadruple bolus, insulin-induced hypoglycemia and metyrapone are presented in Tables 1, 2 and 3 and combined data in all the subjects in Figure 1.

Quadruple Bolus

The serum cortisol rise was modest (5.6 μg per dl in men and 7 μg per dl in women). The difference from baseline values was significant at all times in men but only at 90 minutes in women. A negligible increase in the plasma ACTH level occurred. An increment in the plasma ACTH value of greater than 65 pg per ml did not occur in any of the subjects, and only seven had an increment of 20 pg per ml or greater. The serum LH and FSH levels increased significantly with

TABLE 1.—*Serum Cortisol, Luteinizing Hormone (LH), Follicle-Stimulating Hormone (FSH), Thyrotropin (TSH), Growth Hormone, Prolactin and Plasma Adrenocorticotropic (ACTH) Levels in Ten Normal Male Subjects and Five Normal Female Subjects Following a Single-Bolus Intravenous Administration of Corticotropin-, Growth Hormone-, Gonadotropin- and Thyrotropin-Releasing Hormones* *

Hormone, Mean (SEM)	*Time (Min)*						
	0	*15*	*30*	*45*	*60*	*90*	*120*
Cortisol (μg/dl)							
Men	15.3	18.5†	20.2†	21.0†	20.9†	19.1†	18.2†
	(0.8)	(0.9)	(0.9)	(1.2)	(0.9)	(0.8)	(0.9)
Women	13.2	15.2	17.4	18.4	20.2	20.0†	18.8
	(1.5)	(2.6)	(3.0)	(3.2)	(3.7)	(3.3)	(3.3)
Normal range, 13.5-18							
ACTH (pg/ml)							
Men	54	60	63	62	58	59	62
	(5.7)	(6.7)	(7.1)	(3.3)	(4.8)	(6.6)	(7.9)
Women	74	81	72	79	83	84	77
	(5.3)	(6.0)	(7.6)	(7.6)	(10.6)	(9.7)	(9.2)
Normal range, 0-82							
LH ‡ (mIU/ml)							
Men	7.4	66†	78†	70†	63†	52†	44†
	(0.9)	(12.3)	(12.1)	(9.7)	(7.6)	(6.0)	(5.1)
Women	9.8	30†	43†	45†	45†	55†	60†
	(4.5)	(9.9)	(11.1)	(10.7)	(9.0)	(12.4)	(16.5)
Normal range, men: 3.8-22.6, women: 3.6-29.4							
FSH‡ (mIU/ml)							
Men	9.8	12.5	14.8†	15.8†	15.9†	16.0†	12.7
	(2.2)	(2.3)	(2.4)	(2.5)	(2.6)	(2.6)	(2.4)
Women	9.5	11.0	12.8†	14.0†	15.0†	18.8†	21.8†
	(1.5)	(1.6)	(1.4)	(0.8)	(0.7)	(1.9)	(3.6)
Normal range, men: 1.5-18.6, women: 2.8-17.2							
TSH (μU/ml)							
Men	2	10†	11†	10†	8†	6†	5†
	(0.4)	(1.3)	(1.5)	(1.2)	(1.3)	(1.1)	(1.2)
Women	2	10†	11†	10†	9†	7†	5†
	(0.4)	(2.0)	(2.3)	(2.0)	(2.3)	(2.1)	(1.6)
Normal range, 0-10							
Growth hormone (ng/ml)							
Men	1	15†	24†	23†	18†	8†	5†
	(0.1)	(2.6)	(4.5)	(5.0)	(4.9)	(2.4)	(2.4)
Women	4	17†	28†	32†	21†	10	5
	(1.8)	(2.9)	(8.6)	(7.8)	(4.5)	(2.9)	(1.3)
Normal range, 0-5							
Prolactin (ng/ml)							
Men	9	43†	35†	28†	23†	15†	12†
	(1.1)	(4.2)	(3.6)	(3.0)	(2.5)	(1.6)	(1.5)
Women	11	69†	60†	47†	36†	22†	17†
	(0.5)	(11.5)	(10.8)	(10.0)	(7.1)	(4.7)	(3.0)
Normal range, 0-18.5							

SEM = standard error of the mean

*Dosages of the quadruple injection were as follows: CRH, 1.5 μg/kg; GRH, 1.5 μg/kg; GnRH, 2 μg/kg, and TRH, 3 μg/kg.

†$P < .05$ for difference from baseline.

‡The data from one postmenopausal woman were excluded from LH and FSH calculations.

peaks between 30 and 120 minutes. Serum TSH, growth hormone and prolactin levels also increased significantly, with the highest values between 15 and 30 minutes.

Symptoms or Side Effects

Nearly all of the subjects had a flushed feeling within the first minute of the injection. No clinically significant (greater than 10 mm of mercury) change in blood pressure was noted and no symptoms persisted for more than five minutes after the injection. The 20-channel chemistry test, complete blood count and analysis of urine done before and after each test failed to elicit any abnormalities.

Insulin-Induced Hypoglycemia

All subjects tested showed hypoglycemia (less than 35 mg per dl) after insulin injection. The mean nadir glucose (30 minutes) was 22.6 mg per dl in women and 27.4 mg per dl in men. A sixfold increase in serum growth hormone and a greater than threefold increase in serum prolactin were observed in men and women.

All subjects had symptoms during the glucose nadir. In decreasing order of frequency, these included light-headedness, sweating, hunger, nausea, flushing, somnolence and palpitations. In addition, several subjects had fatigue and malaise persisting for one to four hours after the end of the study.

Metyrapone Test

Both men and women showed a greater than 10 μg per dl decrease in serum cortisol eight hours after metyrapone and a greater than 100 pg per ml increase in plasma ACTH, with the plasma 11-deoxycortisol level reaching a mean of 19 μg per dl in women and 24 μg per dl in men. These mean increments were all statistically significant. One person had mild nausea after ingesting the metyrapone.

TABLE 2.—*Serum Cortisol, Growth Hormone, Prolactin and Plasma Adrenocorticotropic Hormone (ACTH) Levels Following Intravenous Injection of Regular Insulin (0.1 U/kg) in Ten Normal Male and Five Normal Female Subjects*

Hormone, Mean (SEM)	*Time (Min)*				
	0	*15*	*30*	*45*	*60*
Cortisol (μg/dl)					
Men	15.8	14.1	16.1	21.5*	24.5*
	(1.2)	(1.3)	(2.2)	(1.4)	(0.8)
Women	15.6	13.8	13.8	18.4	21.6*
	(2.5)	(2.0)	(2.0)	(2.0)	(1.5)
	Normal range, 13.5-18.0				
ACTH (pg/ml)					
Men	67	61	98*	125*	91*
	(6.5)	(5.1)	(4.2)	(7.3)	(7.6)
Women	68	58	88	123	107
	(7.2)	(7.2)	(17.7)	(31.0)	(20.6)
	Normal range, 0-82				
Growth Hormone (ng/ml)					
Men	0.5	1*	7*	24*	34*
	(0.2)	(1.3)	(3.3)	(5.5)	(6.9)
Women	3	3	9*	14*	17*
	(1.4)	(1.4)	(3.3)	(4.6)	(4.9)
	Normal range, 0-5				
Prolactin (ng/ml)					
Men	8	7	8	24*	23*
	(0.8)	(0.9)	(1.2)	(3.5)	(3.5)
Women	12	10	18	45	49
	(1.5)	(0.7)	(7.7)	(28.8)	(34.0)
	Normal range, 0-18.5				

SEM = standard error of the mean

*$P < .05$ for difference from baseline.

Discussion

Evaluating pituitary function is a common practice in the diagnosis of hypopituitarism. This could well involve the use of separate or combined injections of TRH and GnRH, an overnight metyrapone test and an insulin-induced hypoglycemia test with its attendant unpleasant side effects. We have shown that prolactin, growth hormone, TSH, FSH, LH and cortisol can be stimulated effectively by a single injection of four hypothalamic peptides and that this can be done within a two-hour period with only minimal transient side effects and without admission to hospital. The growth hormone response was comparable and prolactin response was greater than that produced by insulin hypoglycemia. Serum cortisol but particularly plasma ACTH responses to both tests were characterized by a striking variability. Metyrapone administration on the other hand elicited a clear-cut ACTH and 11-deoxycortisol response.

There are several possible explanations for the small plasma ACTH and serum cortisol increments after CRH administration. The first is that the relatively high baseline cortisol levels had an inhibitory effect on pituitary responsiveness to CRH, as has been suggested by Hermus and co-workers.[12] Another possibility is that our dose of 1.5 μg per kg of body weight of CRH, which is 0.5 μg per kg over the half maximal response dose reported by Orth and colleagues, was insufficient to effect a reproducible response.[13] This could have occurred because of a relatively decreased potency of the CRH that we used compared with that obtained from other sources. In vivo or in vitro interactions between the peptides seem an unlikely explanation because some persons had as

TABLE 3.—*8 AM Serum 11-Deoxycortisol and Cortisol and Plasma Adrenocorticotropic (ACTH) Levels Following Oral Administration of 3.0 Grams of Metyrapone at Midnight the Previous Day. Data in Ten Normal Male and Five Normal Female Subjects*

Hormone, Mean (SEM)	*Baseline*	*Postmetyrapone*
Cortisol (μg/dl)		
Men	15.6	2.4*
	(1.0)	(0.6)
Women	12.4	1.7*
	(2.8)	(0.2)
	Normal range, 13.5-18.0	
ACTH (pg/ml)		
Men	71	176*
	(6.5)	(11.9)
Women	73	284*
	(9.0)	(38.5)
	Normal range, 0-82	
11-Deoxycortisol (μg/dl)		
Men	—	24
	—	(2.0)
Women	—	19
	—	(5.9)
	Normal range, postmetyrapone >7.0	

SEM = standard error of the mean

*$P < .05$ for difference from baseline.

much as a 33 pg per ml increase in ACTH and a 17 μg per dl increase in cortisol, even though the peptides were prepared in an identical manner and injected into a homogeneous group of subjects. Furthermore, other investigators have failed to find any difference in hormonal response to insulin, TRH and GnRH when it is injected individually as compared with simultaneous administration.[10] In addition, work reported in a recent abstract[9] showed no interactions between TRH, GnRH, GRH and CRH when the hormone response to separate injections was compared with that of simultaneous administration. In contrast to our findings, however, those investigators reported an increase in ACTH in response to CRH. Because of cost, discomfort to the subjects and the availability of these previous reports, we elected not to inject each of the peptides individually. However, we did inject four normal persons with CRH alone and found similar unimpressive ACTH and cortisol responses to those seen with our quadruple injection (data not shown). It is important to point out that other investigators have found only modest increases in plasma ACTH after CRH administration in normal persons, with mean increments of 20 to 65 pg per ml.[3,12-16]

The plasma ACTH response to the overnight metyrapone test was greater than that to the peptide bolus and exceeded that reported by others to CRH alone. This is very likely due to the prolonged ACTH stimulation obtained from metyrapone administration and suggests that this test is a more reliable method for studying ACTH function than the single-pulse stimulation with CRH as reported to date. Orth has pointed out the unexplained variability in response to CRH in patients with Cushing's disease, even when baseline cortisol is considered.[14] It is possible that such variability may be eliminated by combining CRH with vasopressin, which produces a much greater cortisol and ACTH increment than either alone.[15]

In summary, we have found that the four hypothalamic peptides CRH, GRH, GnRH and TRH can be safely administered together to normal subjects, and that they can be used to study the pituitary secretion of FSH, LH, TSH, prolactin and growth hormone but not ACTH. In our hands, administering CRH intravenously does not reliably elicit a pituitary ACTH response in subjects known to have normal ACTH reserve by other means. We found that the overnight metyrapone test produced a greater and more reliable ACTH response than the quadruple injection or the insulin hypoglycemia test. We conclude that a triple injection of TRH, GnRH and GRH, although not evaluated directly in this study, is an effective stimulus for all the clinically significant pituitary hormones except ACTH, which is better stimulated by metyrapone than by CRH. Further studies using a triple injection of TRH, GnRH and GRH to evaluate hormone response in hypopituitary patients will be necessary to establish that this test can be clinically useful.

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Endoscopic Neodymium-YAG Laser Treatment of Nonresectable Gastrointestinal Tract Cancer

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Five patients with advanced gastrointestinal tract cancers were treated endoscopically with the neodymium-YAG infrared laser. Palliative ablation of an obstructing or hemorrhaging intraluminal malignant lesion was safely achieved in all patients.

(Cello JP, Melnick J, Meiselman MS: Endoscopic neodymium-YAG laser treatment of nonresectable gastrointestinal tract cancer. West J Med 1985 Jan; 142:42-44)

For most patients with nonresectable obstructing or hemorrhaging gastrointestinal tract cancer, a palliative operation is the treatment of choice. In many instances, however, because of advanced progression of disease or because of patient refusal to accept surgical resection, malignant lesions of the gastrointestinal tract can present management problems due to high-grade obstruction and recurrent hemorrhage. Direct or indirect dilation with bougies may serve temporarily to relieve obstruction in the esophagus. Additionally, endoscopically or surgically placed esophageal stents, such as the Celestin tube, will allow ingestion of a liquid diet.[1] Nonresectable rectal tumors have been treated for decades with electrofulguration through a rigid sigmoidoscope.[2] Most recently, in a few centers, the neodymium-yttrium-aluminum-garnet (Nd-YAG) laser has been used in palliative ablation of obstructing tumors of the gastrointestinal tract. Experience with this treatment modality has been the subject of a limited number of research papers. Five patients with large bulky tumor masses of the gastrointestinal tract (three rectal and two esophageal) have been treated at San Francisco General Hospital Medical Center and are the subject of this article.

Patient Population

All patients were treated at the San Francisco General Hospital Medical Center. The study was approved by the Committee on Human Research of the University of California, San Francisco. Patient treatment was likewise approved by the Food and Drug Administration because the clinical investigators were covered by an investigational device exemption issued to the United States distributor of the laser (Endo-Lase, Inc, Washington, DC).

Methods

Endoscopic laser therapy was carried out on an inpatient or outpatient basis. In all instances, the treatment program was initiated on an inpatient basis. The endoscopic procedure was done using a GIF-IT fiberoptic endoscope (Olympus Corporation of America, New Hyde Park, New York) or a TCF-1S flexible sigmoidoscope. The patients were premedicated with meperidine hydrochloride and diazepam given intravenously. The Medilas-2 Nd-YAG laser (manufacturer, Messerschmitt-Bolkow-Blohm, Munich, Germany), with an infrared-beam power adjustable from 15 to 100 W, was used. The leading margin of the tumor mass was approached endoscopically and the pilot laser, a 2-mW helium-neon laser (wavelength 630 nm) was used to identify the treatment area. The laser power was set at between 70 and 90 W, using an external power meter. Treatment was applied in pulses of from 0.5 to 5 seconds. Carbon dioxide was used coaxially both to cool the quartz-fiber guide of the laser and to clear the treatment area of debris and smoke. Treatment was confined initially to the intraluminal presenting margin of the tumor. After a delay of several days to allow for tissue sloughing, a repeat treatment was carried out on either an inpatient or outpatient basis. In general, several treatment sessions were needed to destroy completely all visible intraluminal tumor and to relieve obstructive symptoms.

Results

Five patients with nonresectable gastrointestinal tract carcinoma (three rectal and two esophageal), ranging in age from 62 to 89 years, were evaluated and treated. Table 1 shows the tumor location, histologic type, extent of tumor involvement, degree of luminal occlusion and major patient disability. Two patients (1 and 4) with large tumor masses of the rectum had refused proctectomy and colostomy in spite of extensive counselling by a number of health care providers. Radiation therapy was undertaken in these patients; however, tumor progression became clinically incapacitating. The third patient with rectal cancer, patient 2, had undergone a palliative

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TABLE 1.—*Clinical Presentation and Tumor Characteristics*

Patient	*Age (Yrs), Sex*	*Tumor Location*	*Histologic Type*	*Tumor Length (cm)*	*Luminal Occlusion (%)*	*Major Disability*	*Previous Radiation Therapy*
1	83 ♂	Rectum	Adenocarcinoma	5	75	Obstruction, bleeding (4 units)	Yes
2	63 ♂	Rectum	Adenocarcinoma	15	50	Massive hemorrhage (13 units)	Yes
3	63 ♀	Esophagus	Squamous cell carcinoma	7	100	Obstruction	Yes
4	89 ♂	Rectum	Adenocarcinoma	5	50	Obstruction, bleeding (2 units)	Yes
5	62 ♀	Esophagus	Squamous cell carcinoma	7	80	Obstruction	No

low anterior resection, but a bulky tumor recurrence developed and the patient had anastomotic breakdown with pelvic abscess formation. He was readmitted with profuse rectal bleeding and signs of sepsis. The two patients with esophageal squamous cell carcinoma (patients 3 and 5) were noted to have high-grade obstruction of the upper thoracic esophagus. In both instances, computed tomographic scanning showed extensive involvement of the mediastinum, including invasion of the aorta and encroachment of the trachea. One of these patients, patient 3, had undergone prior radiation therapy and multiple attempts at direct and indirect dilation of the tumor. Despite this, she had total obstruction and was unable to handle secretions. The second patient with esophageal cancer, patient 5, had been able to consume only a liquid diet and at the time of initiation of treatment with the Nd-YAG laser weighed only 36 kg (80 lb).

As noted in Table 1, four patients were treated primarily because of high-grade luminal occlusion. Two of these pa-

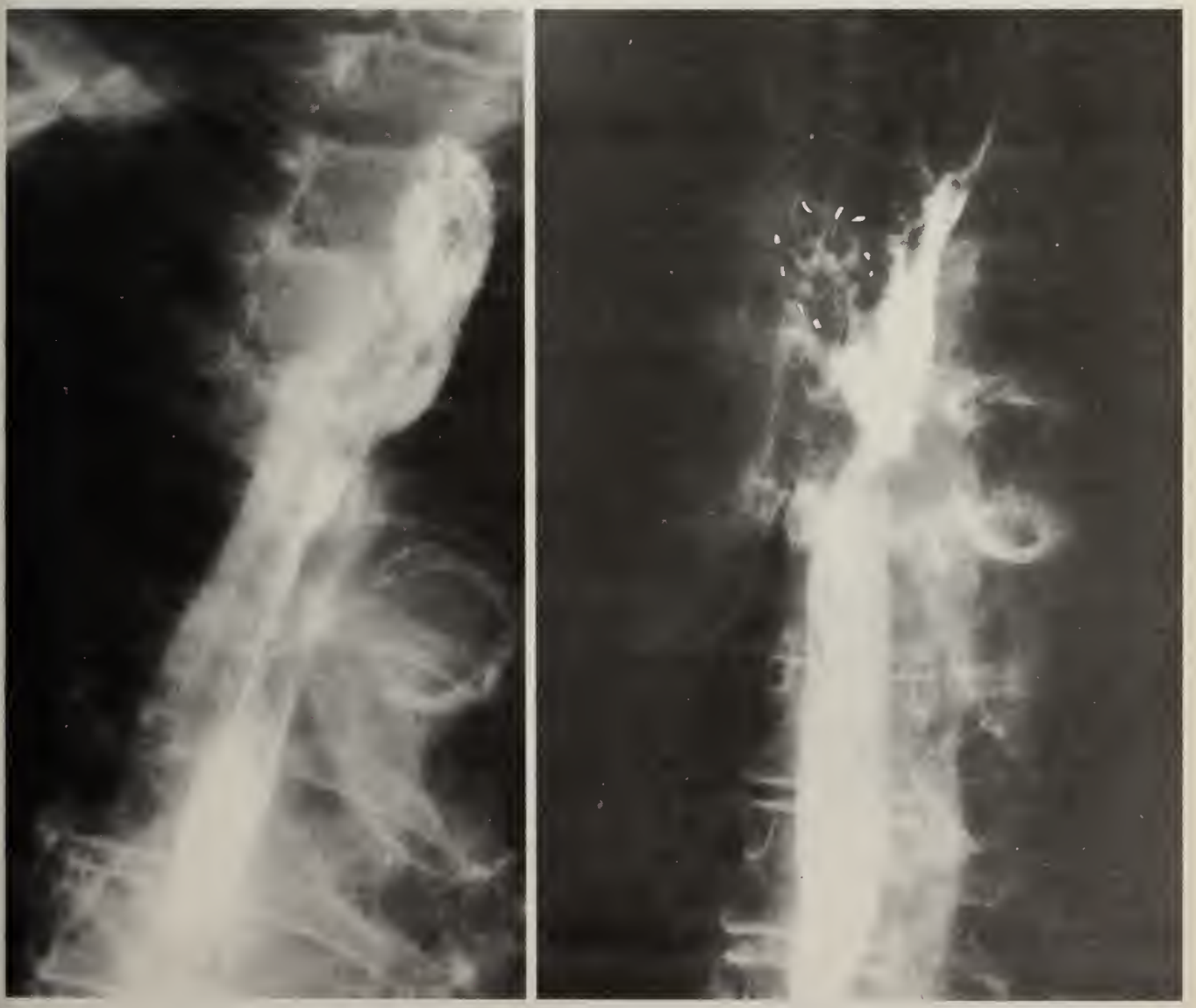

Figure 1.—Left, Esophagogram of patient 3 before Nd-YAG laser ablation of tumor. A large esophageal intraluminal mass is identified at the level of the aortic arch. **Right,** Patient 3 after laser ablation of the esophageal tumor. The intraluminal mass has largely disappeared allowing for passage of barium. A small sinus tract is shown outlined by dashed white lines.

TABLE 2.—*Neodymium-YAG Laser Treatment Programs*

Patients	*Number of Treatments*	*Time Span (days)*	*Mean Energy/ Treatment (joules)*	*Total Energy (joules)*
1	2	15	3,923	7,846
2	1	1	10,000	10,000
3	4	9	1,639	6,558
4	2	3	6,909	13,819
5	3	13	2,527	7,582

tients also had moderately severe gastrointestinal tract hemorrhage. Patient 2 had primarily exsanguinating lower gastrointestinal tract hemorrhage.

The patients received one to four Nd-YAG laser treatments, spanning from 1 to 15 days. All patients were initially treated in hospital. If satisfactory progress was noted by the end of the second treatment session, the patients were discharged and subsequent treatments continued on an outpatient basis. Table 2 shows the treatment energies, ranging from 6,500 to 14,000 watt-seconds (joules) of infrared energy.

All patients had substantial improvement of their condition following completion of the Nd-YAG laser treatment. The patient with massive rectal hemorrhage ceased bleeding completely and required no further transfusions throughout the remainder of the hospital stay. Within a week following treatment, however, this patient died of the Gram-negative bacterial sepsis with which he was admitted originally. The two patients with obstructing rectal tumors, patients 1 and 4, have remained free of high-grade obstruction and hemorrhage for two to four months. The two patients with near-total occlusion of the esophageal lumen have had remarkably reduced objective and subjective obstruction for two to four months follow-up. Radiographically, luminal patency of at least 8 mm was achieved in both patients (Figure 1). In addition, they have resumed near normal dietary intake, with 4.5 to 7 kg (10 to 15 lb) of weight gain.

One possible complication developed in conjunction with Nd-YAG laser treatment. Patient 3 reported paroxysms of coughing following ingestion of liquids three weeks after completion of laser therapy to an esophageal lesion. Barium radiography showed a blind-ending sinus tract proximal to the area of luminal narrowing (Figure 1). Several attempts failed to show an esophagotracheal fistula. Follow-up endoscopy showed mucosal ulceration with benign findings on biopsy. The patient responded to a direct dilation of this strictured area and has resumed normal food intake.

Discussion

The word *laser* is an acronym for "*l*ight *a*mplification by the *s*timulated *e*mission of *r*adiation." The energy radiation is coherent, intense, highly directional and monochromatic. The energy produced by the neodymium-yttrium-aluminum-garnet crystal is the infrared spectrum, with a wavelength of 1,060 nm and a depth of penetration limited to 3 mm. At about 0.5 cm from the distal tip of the quartz-fiber guide, a spot size of little more than 1 mm in diameter focuses the energy of the laser onto a precise tissue target. With endoscopic control, the beam is easily targeted.

The neodymium-YAG laser has been used in conjunction with flexible fiberoptic endoscopy in the treatment of bleeding gastrointestinal tract lesions such as ulcers, gastritis and angiodysplasia.[3] More recently, this laser, whose energy transmits efficiently through a 600-micron diameter quartz fiber, has been used endoscopically to treat obstructing and hemorrhaging gastrointestinal tract cancers.[4-7] In one report, Fleischer and Kessler treated 14 patients with tumors of the esophagus ranging in length from 5 to 11 cm.[4] In 11 of these patients, luminal occlusion before treatment was in excess of 90%. With from 2 to 13 treatment sessions over a mean of 11.6 days, all 14 patients had clinical, endoscopic and radiographic evidence of improvement. Only two complications that might be attributed to the laser therapy occurred. Mellow and co-workers likewise reported Nd-YAG laser therapy for far-advanced esophageal carcinoma in 11 patients in whom other methods had failed.[5] With a mean of 3.3 treatments, 10 of 11 patients had significant resolution of dysphagia. In one patient, however, a tracheoesophageal fistula developed concomitant with laser treatment. In one additional patient, a preexisting tracheoesophageal fistula was treated first by enlarging the lumen with laser therapy and then by placing a stent endoscopically.

Lambert and Sabben treated 40 patients with large adenocarcinomas of the rectum.[6] Symptomatic relief was obtained immediately for bleeding or anal protrusion in all patients. Bowers and Dixon used the Nd-YAG laser in seven patients who had colorectal cancer.[7] All tumors were significantly reduced in size with hemorrhage and obstruction controlled in nearly all patients.

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Management of Community-Acquired Pneumonia in Outpatients

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The medical records of 94 patients with pneumonia who were not admitted to hospital were reviewed and compared with those of 25 patients admitted to hospital for treatment of pneumonia. In all, 93% of the outpatients in whom follow-up could be obtained did not require modification of treatment. This included patients older than 50 years of age without important underlying illness, patients with leukocyte counts of more than 14,000 per μl and patients with multilobular pneumonia. A properly obtained Gram-stained sputum specimen showing a predominant organism was the best method for determining the antimicrobial regimen. If sputum cannot be obtained for Gram's staining, erythromycin should be the drug of choice for patients younger than 40 years and ampicillin or erythromycin should be given to those patients older than 40 years who are managed outside of the hospital. Patients who are critically ill with tachypnea or hypoxia and those with severe underlying illness and pneumonia should be admitted to hospital.

(Siegel D: Management of community-acquired pneumonia in outpatients. West J Med 1985 Jan; 142:45-48)

Despite the use of antimicrobial drugs, pneumonia continues to be a major cause of morbidity and mortality. It is currently the seventh most common cause of death in the United States and disease of the respiratory system is the sixth leading discharge diagnosis.[1] Hospital-acquired pneumonia, pneumonia in immunologically compromised hosts and new or unusual infectious agents causing pneumonia are popular subjects for clinical discussion and investigation.[2,3] There have been few reviews of large numbers of patients with community-acquired pneumonia. Such basic issues as hospital admission criteria for patients with pneumonia and preferred antimicrobials for management of pneumonia in outpatients have received little attention.

In this report, the experience at San Francisco General Hospital with the management of pneumonia in ambulatory outpatients is reviewed. Factors that correlated with a satisfactory outcome are identified, and an approach to antimicrobial drug selection is proposed. The financial savings in the management of pneumonia, outpatient versus inpatient, are calculated.

Patients and Methods

The study group consisted of patients seen in the Emergency Department of San Francisco General Hospital Medical Center, an acute care public hospital that serves as a major teaching hospital for the University of California, San Francisco. A computerized retrieval system was used to identify charts of consecutive patients with a diagnosis of pneumonia who were seen in the Emergency Department from July 1979 through December 1980 and who were treated as outpatients. All patients included in the analysis had a clinical history consistent with pneumonia and an infiltrate on the chest roentgenogram. Evaluation of outcome of therapy was based on either a return clinic visit or a telephone discussion. The charts of 25 patients seen in the Emergency Department during the same period of time who were admitted to hospital with a primary diagnosis of pneumonia were randomly selected from a computerized list. These patients were compared with patients with pneumonia who were not admitted to hospital in an attempt to identify those factors that favored

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TABLE 1.—*Comparison of Clinical Characteristics of Inpatients and Outpatients With Pneumonia*

	*Inpatients** N = 25	*Outpatients** N = 94	*P value*
Age (yr)	55.4 (25)	35.1 (94)	< .001
Sex	♂ 88% - ♀ 12%	♂ 61% - ♀ 39%	
Underlying illness	100%	14%	< .001
Temperature (°F)	100.6 (21)	100.3 (93)	ND†
Pulse (beats/min)	111.4 (24)	96.1 (87)	< .001
Respiratory rate (breaths/min)	28.8 (17)	20.4 (71)	< .001
1 Lobe	44%	80%	< .005
> 1 Lobe or 1 lobe + pleural effusion	56%	20%	< .005
Leukocyte count (/μl)	14.4 (25)	12.2 (70)	< .025
P_{CO_2} (torr)	32.4 (24)	32.3 (21)	ND†
P_{O_2} (torr)	61.8 (24)	72.0 (21)	< .0025
Duration of hospital stay (days)	9.5 (25)		

P_{CO_2} = partial carbon dioxide pressure, P_{O_2} = partial oxygen pressure

*Mean value for number of patients (shown in parentheses).

†ND = no difference.

admission to hospital and factors that affected the outcome of therapy.

Nonparametric data were analyzed by the χ^2 test with Yates's correction. Parametric data were analyzed by Student's *t* test.

Results

Comparison of Inpatients and Outpatients With Pneumonia

The charts of 94 patients with pneumonia who were treated on an outpatient basis were reviewed. The data were compared with those of 25 patients admitted to hospital for treatment of their pneumonia; the clinical characteristics are summarized in Table 1. Both groups had a predominance of male to female patients. The mean age of inpatients was greater than that of the outpatients. Temperature was similar between the two groups, but pulse and respiratory rates were significantly higher in the inpatient group. The mean leukocyte count in the inpatient group was also significantly higher than in the outpatient group. The carbon dioxide partial pressure of arterial blood was similar in both groups, but the oxygen partial pressure (P_{O_2}) was significantly lower in the patients in hospital. The amount of lung involved and the presence of underlying illness were compared: The incidence of more than one lobe or one lobe and an associated pleural effusion was significantly greater in the in-hospital patients. All patients in hospital had an important underlying illness compared with only a small percentage in the outpatient group (Table 2).

Results of Treatment of Pneumonia in Outpatients

Of the patients with pneumonia not admitted to hospital, follow-up was achieved in 69 (73%); the condition of 64 (93%) was improved two to seven days after the diagnosis of pneumonia and did not require modification of the therapy prescribed in the Emergency Department. Two additional patients were seen at our hospital who had not responded to therapy prescribed at another institution.

Of the seven patients requiring modification of therapy (Table 3), nausea and vomiting developed in one after erythromycin therapy; the patient was switched to penicillin treatment and improved clinically. In the other six patients, three were given tetracycline, but when no resolution of clinical symptoms resulted, erythromycin was substituted and all three did well. Two outpatients requiring modification of therapy were originally treated with penicillin. At follow-up when clinical improvement did not occur, one was switched to erythromycin therapy and recovered, and the other was admitted to hospital and treated with ampicillin with satisfactory results. One patient was initially treated with erythromycin, but when her condition did not improve the next day, she elected to transfer to another hospital and subsequently recovered.

Several factors in patients managed on an outpatient basis were analyzed independently to determine if they had an adverse impact on outcome (Table 4). Age older than 50 years without underlying illness, involvement of more than one lobe of the lung and a leukocyte count of more than 14,000 per μl appeared to have no adverse effects on outcome. The number of patients with severe underlying illness and pneumonia managed as outpatients was too small to be analyzed.

TABLE 2.—*Underlying Illness*

Group of Patients	*No. of Patients*	*No. of Patients With*							
		Diabetes	*Alcoholism*	*Chronic Pulmonary Disease*	*Intravenous Drug Abuse*	*Cancer*	*Cardiac Disease*	*Other*	*Total (%)*
Inpatient	25	2	8	9	3	1	1	2	100
Outpatient	94	1	1	5	2	0	1	3	14

TABLE 3.—*Outpatients With Pneumonia Who Required Modification of Treatment*

Patient No.	*Sex*	*Age, yr*	*Temperature °F*	*Pulse beats/min*	*Respiratory Rate breaths/min*	*Leukocyte Count /μl*	*No. of Lung Lobes Involved*	*Initial Antimicrobial Therapy*	*Follow-up*
1	♂	18	101.2	--	--	17.2	1	Erythromycin	Nausea and vomiting; switched to penicillin
2	♂	23	101.2	84	16	19.7	1	Tetracycline	Switched to erythromycin and did well
3	♀	23	100.0	104	18	14.5	1	Tetracycline*	Switched to erythromycin and did well
4	♂	24	103.0	100	24	15.0	1	Tetracycline*	Switched to erythromycin and did well
5	♂	52	100.2	68	18	9.8	2	Penicillin	Admitted and treated with ampicillin
6	♂	28	99.8	100	20	14.5	1	Penicillin	Switched to erythromycin and did well
7	♀	17	102.6	148	12	16.9	1	Erythromycin	Admitted to another hospital

* Given tetracycline at another institution. Other data at our hospital after tetracycline failure.

Antimicrobial Treatment of Outpatients

Erythromycin was the commonly prescribed antimicrobial in outpatients, followed by penicillin and ampicillin (Table 5). One of the problems with erythromycin occurred in a patient who had mixed flora in Gram-stained sputum.

Adequate sputum specimens were obtained and stained with Gram's stain in 42 patients. The results are summarized in Table 6. Five patients had a predominance of small pleomorphic Gram-negative rods and were treated with ampicillin. The ten patients shown to have mixed flora received penicillin, ampicillin or erythromycin. Two of the 42 patients required modification of their treatment regimen.

Discussion

During the past two decades, the nation's health care bill has risen rapidly at an average rate of 11.7% per year. In 1980, health care expenditures in the United States totaled $247.2 billion, an average of $1,067 per person.[4] During the same period, the gross national product rose an average rate of 8.6%. Consequently, national health expenditures have been claiming an increasing share of the gross national product, reaching 9.4% in 1980. An important factor in the growth of expenditures for health care has been the growth of the hospital sector. Hospital care expenditures, traditionally claiming the largest share of the health care dollar, have increased from about 30% of total expenditures in 1950 to 40% in 1980.[5]

The average duration of hospital stay for patients with pneumonia has decreased from 12.1 to 9.5 days in two university hospitals and from 11.6 to 7.1 days in two community hospitals during the decade of 1964 to 1974, with a corresponding decrease in the hospital costs.[6] Neither Sheeley and Sherman nor others have evaluated the need for hospital care of patients. At San Francisco General Hospital the cost of inpatient care is about $400 per day for a bed in a nonintensive care unit, routine laboratory tests and physicians' fees. If the outpatients with pneumonia in this study were admitted to hospital and had an average stay of four days, which is less than half the average stay of 9.5 days for the 25 inpatient cases we evaluated, the average cost would be $1,600 per patient.

Because pneumonia when treated properly has a favorable outcome, it would be important not to attempt to treat patients outside the hospital if they did not do well. In this series, 93% of the outpatients in whom follow-up could be obtained did not require modification of treatment. This group included a high degree of successful therapy even for patients older than 50 years, patients with multilobular pneumonia and patients with leukocyte counts of greater than 14,000 per μl. Because the patients who returned for a follow-up visit were clinically similar to those who did not, I believe that my conclusions would be the same with 100% follow-up, although I cannot be certain of this in a retrospective study of this type. It is also possible that these patients went to other health providers for additional care. However, many of the patients who could not be reached for follow-up were medically indigent and they would not be likely to receive care in other institutions.

The patients treated in hospital for pneumonia had a much greater incidence of underlying illness than the outpatients (100% versus 14%). There were not enough outpatients with underlying illness to determine that these patients would have a poor prognosis when managed outside of the hospital. At the present time, however, the presence of major underlying illness should remain an important criterion for admission to hospital for patients with pneumonia. No other independent variable that was predictive of a poor prognosis with proper medical therapy could be identified. In this context, however, the clinical judgment of the patient's physician is necessary to identify an extremely ill patient who should be admitted to hospital. Leukopenia, evidence of extrapulmonary involvement, signs of circulatory collapse or hypoxia with a Po_2 of less than 60 torr should remain criteria for hospital admission.

The choice of an antimicrobial drug for the treatment of pneumonia in outpatients should depend on the bacterial cause of the infection. At present, Gram's stain of expectorated sputum is the most rapid method for predicting the bacterial cause of pneumonia.[7] Based on the results of this study, a good choice of therapy is penicillin if Gram-positive diplococci predominate consistent with *Streptococcus pneumoniae*. Ampicillin should be used if small pleomorphic Gram-negative rods predominate consistent with *Hemophilus influenzae*. If the flora are mixed, indicating a mixed infection with *S pneumoniae* and *H influenzae*, ampicillin is a good choice for treatment. Erythromycin is active against *S pneumoniae*, which causes pneumonia in all age groups. It is also active against *Mycoplasma pneumoniae*, which frequently causes pneumonia in older children and young adults.[8] Thus, if a sputum specimen for Gram's staining cannot be obtained in a patient with pneumonia who is younger than 40 years, erythromycin is a good therapeutic choice. In patients older than 40 who have community-acquired pneumonia, if a sputum specimen cannot be obtained

TABLE 4.—*Risk Factors in Outpatients With Pneumonia*

Risk Factor	No. of Patients (n = 94)	Follow-up Obtained (n = 69)	No. of Patients With Satisfactory Results	
			No.	(%)
			64	(93)
Age > 50 years	18	16	15	(94)
Multilobular pneumonia	19	13	12	(92)
Leukocyte count > 14,000/μl	22	19	16	(84)

TABLE 5.—*Antimicrobial Management of Outpatients With Pneumonia*

Antimicrobial Drug	No. of Patients	Follow-up Achieved	Satisfactory Results		Unsatisfactory Results
		No.	No.	(%)	No.
Erythromycin	50	36	34	(94)	2
Ampicillin	13	11	11	(100)	0
Penicillin	29	21	19	(90)	2
Tetracycline	2	1	0	(0)	1

TABLE 6.—*Gram-Stain Analysis of Sputum Specimens From Outpatients*

Gram's Stain	No. of Patients	Antimicrobial Management		Follow-up	Satisfactory Results	
					No.	(%)
Gram-positive diplococci	27	Penicillin	18	17	16	(94)
		Erythromycin	6			
		Ampicillin	3			
Gram-negative rods	5	Ampicillin	5	5	5	(100)
Mixed flora	10	Penicillin	5	6	5	(83)
		Erythromycin	2			
		Ampicillin	3			

for Gram's staining, the choice of an antimicrobial is more difficult. Earlier studies of community-acquired pneumonia base much of the data of bacterial cause on sputum cultures.[9,10] Unless done with extreme care, sputum cultures are an inaccurate way of determining the bacterial cause of pulmonary infections,[11,12] and thus the results of these studies cannot be used to determine which antimicrobial agent to use. Although *H influenzae* appears to be a more common agent causing pneumonia in older patients than previously appreciated,[13] its exact incidence has not been determined. Erythromycin is not consistently active against *H influenzae* in achievable serum concentrations. Although ampicillin-resistant isolates of *H influenzae* have been implicated with increasing frequency in serious infections in children, few cases have been described in adults that include patients with encapsulated strains.[14] Thus, at this time ampicillin remains a good choice if pneumonia due to *H influenzae* is suspected. If ampicillin-resistant infections with *H influenzae* become more common in adults, this recommendation will have to be modified. Erythromycin is the recommended therapy for legionnaires' disease, which usually causes pneumonia in middle-aged or older people.[15] Again the exact incidence of this disease is not known. In this series treatment of outpatients older than 40 years without important underlying illness—in whom a sputum specimen could not be obtained for Gram's staining—with either ampicillin or erythromycin resulted in a satisfactory outcome. *S pneumoniae* and *H influenzae* are frequently resistant to tetracycline and this agent cannot be recommended for the treatment of pneumonia.[16]

In summary, many patients who have pneumonia can be treated successfully out of hospital. This includes patients older than 50 years without underlying disease, patients with leukocyte counts of greater than 14,000 per μl and patients who have multilobular pneumonia. Patients who are critically ill with tachypnea or hypoxia and those with severe underlying disease and pneumonia should be admitted to hospital. A properly obtained Gram-stained sputum specimen showing a predominant organism remains the best method for determining the antimicrobial regimen. If a sputum specimen cannot be obtained for Gram's staining, ampicillin or erythromycin should be the agents of first choice for the management of otherwise healthy ambulatory outpatients with pneumonia. This approach to patients with pneumonia will result in considerable financial savings without sacrificing clinical efficacy.

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The Variable Hyponatremic Response to Hyperglycemia

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Hyperglycemia may lower the plasma sodium concentration. Theoretical analyses have suggested that elevations in glucose concentration produce an invariant hyponatremic response. We propose, however, that change in plasma sodium concentration in response to hyperglycemia is variable and depends on (1) the distribution of total body water and solute, (2) the relationship between the gain of extracellular glucose and the loss of intracellular solute and (3) the intake and loss of solute and water. These factors are incorporated into a formulation of the relationship between the plasma sodium and glucose concentrations.

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Because hyperglycemia may notably reduce plasma sodium concentration, a clinician often must decide whether the reduction is appropriate for the elevation in glucose concentration of the plasma.[1-6] More than 20 years ago it was suggested that sodium concentration would decline approximately 2.8 mEq per liter for each 100 mg per dl rise in glucose concentration above 100 mg per dl.[1,2] Katz rejected this "classic" figure and suggested that the change in sodium concentration varied linearly with the increment in glucose concentration. He calculated the decrement in sodium concentration to be 1.6 mEq per liter per 100 mg per dl rise in glucose concentration.[3] This figure and the analysis from which it was derived are widely accepted.[4-7] In assessing the relationship between hyperglycemia and hyponatremia, however, the answers to several questions will largely determine the correct decrement in sodium concentration. What is the distribution of body solute and water? What is the source of the extracellular glucose that produces hyperglycemia? What other conditions apply? Understanding the limitations inherent in earlier approaches enables us to formulate a more broadly applicable relationship.

Classic Solution

The classic analysis included these assumptions: (1) total body water is 60% of body weight and is distributed two thirds as intracellular fluid (ICF) and one third as extracellular fluid (ECF), (2) glucose and sodium are essentially restricted to the extracellular space, (3) water freely crosses cellular membranes, (4) glucose is "added to" the extracellular space, (5) intracellular solute remains constant, (6) extracellular, and therefore intracellular, osmolality ultimately returns to *normal*—that is, an elevated glucose and a coincidentally depressed sodium concentration[1-3]—and (7) the classic solution does not specify that the increase in extracellular fluid space that occurs in hyperglycemia must be supplied by a positive water balance. It follows that if osmolality is to remain unaltered and intracellular solute is constant, intracellular volume must be static.

Because water traverses cellular membranes easily, the following relationship obtains:

$$\frac{\text{ICF solute (osmole)}}{\text{ICF volume (liter)}} = \frac{\text{ECF solute (osmole)}}{\text{ECF volume (liter)}}. \quad (1)$$

For purposes of calculation and to illustrate the classic solution, the following plasma values will be defined as normal for a 70-kg man: sodium, 140 mEq per liter; glucose, 100 mg per dl (5.5 mosm per liter); osmolality, 285 mosm per kg. Total body water is 42 liters. The ICF has a volume of 28 liters and contains 7,980 mosm. The ECF has a volume of 14 liters and contains 3,990 mosm.

Inserting these values into equation 1, the effect of adding glucose to the extracellular fluid may be expressed as:

$$\frac{7{,}980 \text{ mosm}}{28 \text{ liters}} = \frac{(3{,}990 + G) \text{ mosm}}{(14 + X) \text{ liters}}, \quad (2)$$

where G = milliosmoles of added glucose and X = the additional water (in liters) needed to reestablish normal osmolality. Solving for X (in liters) in terms of G (in milliosmoles),

$$X = 0.0035G.$$

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ABBREVIATIONS USED IN TEXT
ECF = extracellular fluid
ICF = intracellular fluid

The new sodium concentration, P_{Na}, is

$$P_{Na} = 140\left[\frac{14}{(14+X)}\right] \text{mEq/liter.}$$

The new glucose concentration, P_G, is

$$P_G = \left[\frac{G + (5.5)\cdot(14)}{(14+X)}\right] \text{mosm/liter.}$$

The fall in sodium concentration, ΔP_{Na}, is

$$\Delta P_{Na} = [140 - P_{Na}] \text{ mEq/liter.}$$

The increment in glucose concentration, ΔP_G, is

$$\Delta P_G = [P_G - 5.5] \text{ mosm/liter.}$$

The relationship between ΔP_{Na} and ΔP_G may then be calculated. The sodium concentration is reduced 2.75 mEq per liter per 100 mg per dl increase in glucose concentration.

Solution of Katz

Katz correctly observed that simple addition of solute to the body would necessarily produce at equilibrium an osmolality greater than normal. A redistribution of body water from intracellular to extracellular fluid space would not suffice to return osmolality to its original value.[3] In his analysis, Katz assumes the same conditions as for the classic solution with the following exceptions: (1) it is no longer assumed that osmolality remains normal and (2) intake and output are specifically excluded. Solute as glucose is "added to" the extracellular fluid, raising total body solute content. Intracellular water moves to the extracellular compartment until intracellular and extracellular osmolality equilibrate at some higher value. Intracellular solute is still assumed to be fixed, however. The relationship is

$$\frac{\text{ICF solute (osmole)}}{\text{ICF volume} - Y} = \frac{\text{ECF solute (osmole)} + G}{\text{ECF volume} + Y}, \quad (3)$$

where Y represents the volume of intracellular water moving to the extracellular space, and G is the added glucose.

Employing the same normal values as in the classic solution and inserting these into equation 3, Katz's solution may be expressed as

$$\frac{7{,}980}{28 - Y} = \frac{3{,}990 + G}{14 + Y}. \quad (4)$$

Solving for Y in terms of G,

$$Y = \frac{28G}{11{,}970 + G}.$$

While sodium concentration declines approximately 1.6 mEq per liter with each 100 mg per dl increase in glucose concentration, it is apparent that Y, the volume of intracellular water added to extracellular fluid, cannot vary linearly with the increment in glucose concentration and therefore that ΔP_{Na} cannot vary linearly with ΔP_G.

General Solution

We must identify the source of glucose in the extracellular fluid. This is particularly important in the case of an insulinopenic diabetic patient who has ketoacidosis and is unable to eat, and in whom the plasma glucose is often markedly elevated. Glucose is produced *intracellularly*—it is not "added to" the extracellular fluid from an exogenous source. A variety of intracellular substances are consumed or transformed in the production of the glucose that ultimately enters the extracellular space.[8] This represents the movement of intracellular solute to the extracellular aqueous compartment, and it is incorrect to assume that the quantity of intracellular solute remains fixed. A general analysis of the relationship between glucose concentration and sodium concentration should account for volume changes in both intracellular and extracellular solute and water, as well as accommodating the special conditions assumed for both the classic and Katz's solutions. Finally it should be applicable to the clinical setting of diabetic ketoacidosis where knowledge of the sodium-glucose relationship could be of great benefit.

The general expression is

$$\frac{(\text{ICF solute} - G_1)}{(\text{ICF volume} - Y_1)} = \frac{(\text{ECF solute} + G_2)}{(\text{ECF volume} + Y_2)} \quad (5)$$

where

Y_1 = water lost from the ICF (in liters),
Y_2 = water gained by the ECF (in liters),
G_1 = ICF solute loss (in milliosmoles),
G_2 = ECF gain in glucose (in milliosmoles).

(If intake and output are excluded, ECF volume gain equals ICF loss, that is, $Y_1 = Y_2$; G_1 does not equal G_2, however.)

It is more nearly correct to assume in normal humans that 55% of body water (and solute) is intracellular and 45% is extracellular.[9] Using this assumption, Katz's solution would have predicted a decline of 1.4 mEq per liter in sodium concentration for a 100 mg per dl increase in glucose rather than the 1.6 mEq per liter originally calculated. In the 70-kg man used as our example, ICF volume equals 23.1 liters, containing 6,584 mosm; ECF volume equals 18.9 liters and contains 5,386 mosm. Substituting these values into equation 6,

$$\frac{6{,}584 - G_1}{23.1 - Y_1} = \frac{5{,}386 + G_2}{18.9 + Y_2}. \quad (6)$$

Equation 1 and equation 3 may be derived as special cases of equation 5. In the classic solution, ICF solute and water are assumed to be constant—that is, $G_1 = 0$ and $Y_1 = 0$. Applying these values to equation 5 and allowing for the difference in body fluid distribution, equation 2 is derived from equation 5. Katz assumed that there is no intracellular solute loss, or $G_1 = 0$. However, in Katz's solution, water was allowed to shift from the intracellular compartment, $Y_1 \neq 0$. Because intake and output are excluded as factors in Katz's solution, $Y_1 = Y_2$. Applying these conditions to equation 5 while using Katz's assumed body fluid distribution, equation 3 is derived from equation 5.

Osmotic Equivalence of Glucose Precursors

In the absence of glucose intake, extracellular glucose is produced from gluconeogenesis or glycogenolysis.[8,10,11] The major precursors of glucose are amino acids (derived from proteolysis and transamination); lactate and pyruvate (primarily from glycolysis); and glycerol (from lipolysis).[8,10-12] Acetone may also be a precursor of glucose.[13] Although proteins and glycogen are large molecules, their osmotic activity cannot safely be neglected.[8,14] Some (obligate) intracellular water is retained by the osmotic activity of glycogen or protein. One gram of glycogen obligates osmotically approximately 1.6 grams of water.[8,14] Assume that 1 gram of glycogen per 1.6 grams of water is isosmotic—that is, 1 gram of glycogen per 1.6 grams of H_2O is "osmotically equivalent"

to 285 mosm per kg H_2O. Thus 1 gram of glycogen is equivalent to approximately 0.5 mosm. After glycogenolysis, 1 gram (0.5 mosm) of glycogen forms 5.5 mosm of glucose.[11]

Similarly, each gram of intracellular protein obligates approximately 3.3 grams of water.[8,14] Assume that 1 gram of protein per 3.3 grams of H_2O is osmotically equivalent to 285 mosm per kg of H_2O. A gram of protein is equivalent to approximately 1 mosm. When metabolized, protein yields both glucogenic and ketogenic substrates, providing eight amino acid residues per gram of protein, substrates that can be used to generate approximately three milliosmoles of glucose.[11]

If there is no coexistent lactic acidosis, the concentrations of lactate and pyruvate in the diabetic are not much different from normal values.[12,15] Hepatic extraction of these substrates may be more efficient, particularly during ketoacidosis, but there is little evidence to suggest that a major transcellular shift of these metabolites occurs.[8,12,15]

Fat is stored in a milieu that is almost perfectly water-free.[8] Because intracellular fat obligates no water, it has an osmotic equivalence of zero.

Relationship Between the Loss of Intracellular Solute and the Gain of Extracellular Glucose

From the foregoing considerations, the sources of glucose may be estimated in a diabetic patient with ketoacidosis. Assume that no fluids or solids are consumed. Biochemically the patient resembles to some extent a normal person who is fasting except that the rate of glycogenolysis is elevated, not depressed.[12] During ketoacidosis, glucose output from glycogenolysis may equal that from gluconeogenesis.[12,15] For an extracellular glucose gain of 400 mosm, for example, glycogenolysis and gluconeogenesis will each provide approximately 200 mosm. Using determinations of portal vein and hepatic artery blood flow rates and gluconeogenic substrate concentrations, studies of transhepatic substrate fluxes suggest that about half of gluconeogenic glucose is derived from lactate and pyruvate (100 mosm), a sixth from glycerol (33 mosm) and the remaining third (67 mosm) from amino acid residues.[12,13,15-18]

For glycogenolysis to provide 200 mosm of extracellular glucose, the *intracellular solute loss* is

$$\left[\frac{200\ \text{mosm glucose}}{5.5\ \text{mosm glucose/gram glycogen}}\right]\cdot\left[\frac{0.5\ \text{mosm}}{\text{gram glycogen}}\right]=18\ \text{mosm}.$$

For glycerol, lactate and pyruvate, the intracellular osmotic loss is nil. For proteolysis to provide amino acid residues adequate to produce 67 mosm of extracellular glucose, the intracellular solute loss is

$$\left[\frac{67\ \text{mosm glucose}}{3\ \text{mosm glucose/gram protein}}\right]\cdot\left[\frac{1\ \text{mosm}}{\text{gram protein}}\right]=22\ \text{mosm}.$$

Thus the production of 400 mosm of extracellular glucose (G_2) entails the loss of approximately (18 + 22) = 40 mosm of intracellular solute (G_1). Hence, G_1 is approximately one tenth of G_2. It is important to realize that the relationship between G_1 and G_2 depends little on the assumptions regarding the amounts of extracellular glucose derived from each intracellular source. If one source generates less glucose, more will be supplied by a second source, leaving the net intracellular solute loss substantially unchanged. Substituting these values into equation 6,

$$\left[\frac{6{,}584-(G_2/10)}{23.1-Y_1}\right]=\left[\frac{5{,}386+G_2}{18.9+Y_2}\right].$$

Again $Y_1 = Y_2$. Expressing G_2 now simply as G, the ECF gain in glucose, and solving for Y, the volume of water that shifts from the intracellular to the extracellular compartment,

$$Y=\frac{24.9G}{11{,}970+0.9G}. \qquad (7)$$

Equation 7 is nonlinear, as is the expression for the decrement in plasma sodium concentration. Table 1 shows calculations for the change in plasma sodium concentration for several values of plasma glucose concentration in a 70-kg man. The general solution indicates that the plasma sodium concentration will decline in a nonlinear manner, 1.5 to 1.6 mEq per liter for each 100 mg per dl rise in plasma glucose concentration in a 70-kg man.

TABLE 1.—*Demonstration of the Variable Decrement in Sodium Concentration in Response to Hyperglycemia in a 70-kg Man*

Values	*Plasma Sodium Concentrations*		
G (mosm) 100	300	700	1,000
Y (liter) 0.21	0.61	1.38	1.93
ECF volume (liter) 19.1	19.5	20.3	20.8
P_{Na} (mEq/liter) 138.5	135.6	130.5	127
ΔP_{Na} (mEq/liter) 1.5	4.4	9.5	13
P_G (mg/dl) 193	378	721	963
ΔP_G (100 mg/dl) 0.93	2.78	6.21	8.63
ΔP_{Na} to ΔP_G (mEq/liter per 100 mg/dl) 1.61	1.58	1.53	1.51

G = total glucose added to the ECF (see equation 7)
Y = volume of intracellular water shifting to extracellular compartment
ECF = extracellular fluid
P_{Na} = plasma sodium concentration
ΔP_{Na} = decrease in plasma sodium concentration
P_G = plasma glucose concentration
ΔP_G = increase in plasma glucose concentration
Assumptions: Initial values: Total body water, 42 liters; ECF, 18.9 liters; ICF, 23.1 liters, P_{Na}, 140 mEq/liters; P_G, 100 mg/dl (5.5 mosm/kg)

Effect of Intake by Mouth

The assumption that diabetic ketoacidosis develops when nothing is taken in by mouth is not valid for every case. If intake of water and glucose is considered, the general expression of equation 5 still applies, but the gain in ECF volume no longer necessarily equals the loss in ICF volume. The relationship between ICF solute loss and ECF glucose gain also changes. For a given increment in extracellular glucose concentration, exogenous glucose intake reduces the requirement for generating glucose from intracellular sources. Compared to results predicted when water and glucose taken by mouth are excluded, glucose consumption without water results in a diminished loss of ICF solute, less of a reduction in ICF volume and a smaller gain in ECF volume. Consequently, dilution of extracellular sodium is lessened, and the range of values for ΔP_{Na} to ΔP_G ratio is below 1.5 to 1.6 mEq per liter per 100 mg per dl rise in glucose concentration. In contrast, water intake without glucose means a net increase in the gain of ECF volume. Dilution of extracellular sodium is increased, and values for ΔP_{Na} to ΔP_G ratio exceed 1.5 to 1.6 mEq per liter. Intake of *both* glucose and water affects ΔP_{Na} to ΔP_G ratio as a function of tonicity of the fluid added: hypertonic solutions diminish and hypotonic solutions increase the ratio of ΔP_{Na} to ΔP_G.

Effect of Distribution of Body Water and Solute

The distribution of body water before the development of hyperglycemia is also an important variable in the determination of the ratio of ΔP_{Na} to ΔP_G. While equation 7 satisfactorily describes the relationship between an elevated glucose concentration and a depressed sodium concentration because it accounts for the source of extracellular glucose, it assumes a distribution of body water that is initially 55% intracellular and 45% extracellular. There are instances, however, when this assumption is incorrect: for example, in a patient with edema or one who develops ketoacidosis with a diminished extracellular fluid volume. Whatever the distribution of total body water and solute at the onset of diabetic ketoacidosis, the fundamental considerations regarding the shifts of solute and water still apply and may be used to derive a unique curve relating ΔP_{Na} to ΔP_G for each ICF to ECF ratio. In an edematous patient having excess extracellular fluid equal to 15% of body weight, the ΔP_{Na} to ΔP_G ratio would vary from 1.25 to 1.35 mEq per liter per 100 mg per dl of glucose elevation over a range of glucose values. For a hypovolemic patient with a deficiency of extracellular fluid equal to 10% of body weight, the ratio would be 1.8 to 1.9 mEq per liter. The plasma sodium concentration in a hypovolemic patient may be as much as 8 mEq per liter less than that of the edematous patient for the same plasma glucose level, a clinically significant difference. Hence, because of the dependence of ΔP_{Na} to ΔP_G ratio on the prehyperglycemic partitioning of solute and water between ICF and ECF, there is clearly not a *single* decremental sodium value for a given glucose increment. A nomogram that takes these variables into account is depicted in Figure 1.

Whether the losses of extracellular fluid occur before or during the development of hyperglycemia does not affect the applicability of the nomogram in Figure 1. Urinary solute lost during the osmotic diuresis caused by glucosuria has less sodium and more glucose than the same volume of solute in extrarenal losses.[19-21] For a given gain in extracellular glucose, the effect of urinary losses of solute is to elevate the ratio of ΔP_{Na} to ΔP_G between 1% and 10%, a change which can be neglected in the use of the nomogram.

Although the nomogram defines precisely the varying relationship between the plasma concentrations of sodium and glucose, we suggest that clinical application include the following simple guidelines:

1. If the patient in the ketoacidosis is euvolemic, then the original correction factor of Katz may be used for the ratio of ΔP_{Na} to ΔP_G, which is 1.6 mEq per liter sodium concentration per 100 mg per dl glucose concentration.
2. If, as is more likely to be the case, the patient has a depletion in volume, then a value of 2 mEq per liter

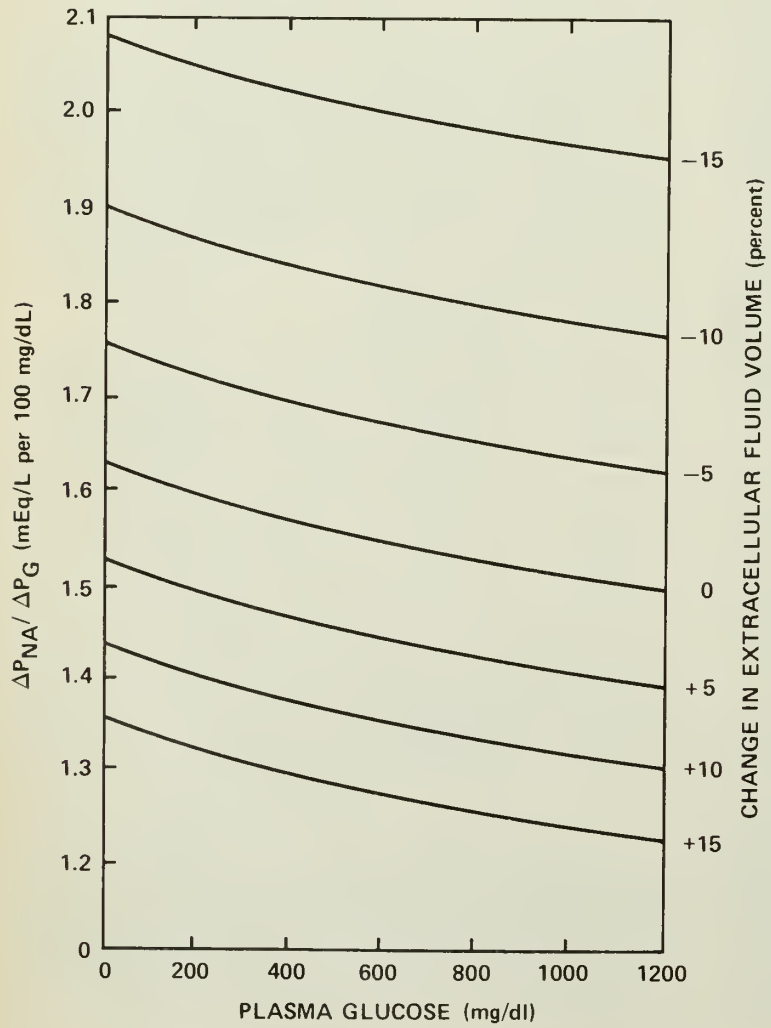

Figure 1.—The decline in plasma sodium concentration ΔP_{Na} (mEq/liter) per increment in glucose concentration ΔP_G (100 mg/dl) is plotted as a function of the glucose concentration and the change from normal in extracellular fluid volume. The abscissa is the plasma glucose concentration. Excess plasma glucose equals this plasma glucose concentration minus 100 mg/dl. The left ordinate is $\Delta P_{Na}/\Delta P_G$. The right ordinate is the estimated change in ECF volume associated with changes in *total body weight* (in percent). To determine $\Delta P_{Na}/\Delta P_G$, locate the intersection of the vertical line determined by the plasma glucose concentration and the curved line determined by the estimate of the change in ECF volume. A horizontal line from the point of intersection to the left ordinate determines the ratio of $\Delta P_{Na}/\Delta P_G$. Multiplying the ratio of $\Delta P_{Na}/\Delta P_G$ by the excess glucose concentration yields the reduction in sodium concentration due to hyperglycemia.

sodium concentration per 100 mg per dl glucose elevation above normal is preferable.

3. Should the patient with ketoacidosis have expanded volume—for example, if the patient has congestive heart failure—a value of 1.2 mEq per liter sodium concentration per 100 mg per dl glucose concentration is a more reasonable correction factor.
4. Finally, it may also be useful to keep these guidelines in mind when confronted by patients with nonketotic hyperglycemic states, although quantitative glucose production has not been studied as thoroughly as glucose production in diabetic ketoacidosis.

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Information Needed for Psoriasis Study

What factors are involved in the origin and course of psoriasis? Researchers in the Department of Dermatology, Stanford University School of Medicine, are examining this question and seek to enlist physicians in an extension of their epidemiologic studies. Physicians are best able to assess certain questions, such as appearance of psoriasis with β-blockers, exacerbation with mental or physical stress, occurrence with arthritis and so forth.

If the journal's readers or family members who have psoriasis will write to Psoriasis, Post Office Box V, Stanford, CA 94305, a short questionnaire will be sent. Responses will be used in the study and the researchers will be pleased to send a report of their findings.

Magnetic Resonance Imaging of the Central Nervous System—An Update

WALTER KUCHARCZYK, MD, FRCP (C); MICHAEL BRANT-ZAWADZKI, MD; DAVID NORMAN, MD, *and* T. HANS NEWTON, MD, *San Francisco*

Magnetic resonance imaging has developed rapidly and now has superior ability to detect and to characterize disease in the central nervous system without any significant biologic hazard. It is becoming the screening method of choice in the diagnosis of neoplasm, ischemia, hemorrhage, infection and degenerative and demyelinating diseases involving the central nervous system.

(Kucharczyk W, Brant-Zawadzki M, Norman D, et al: Magnetic resonance imaging of the central nervous system—An update [Medical Progress]. West J Med 1985 Jan; 142:54-62)

Within a surprisingly short time the quality of magnetic resonance (MR) imaging of the central nervous system has surpassed that of any available imaging modality including computed tomography (CT). Although still in its infancy, this emerging procedure already shows superior ability to define altered tissue constituents when compared with CT and greatly improves the information regarding pathologic processes. Furthermore, the images may be acquired in any desired plane, do not require the use of any ionizing radiation, nor does the procedure damage any biologic tissue. These obvious advantages have helped fuel the development of MR imaging into a viable clinical procedure. Our institution was fortunate in acquiring one of the early clinical instruments and its early use in a hospital setting as applied to the diagnostic evaluation of central nervous system disorders is summarized in this report. For those readers unfamiliar with the fundamental principles underlying MR imaging, a simplified overview follows. Interested readers are referred to more complete discussions of the physics and instrumentation of MR imaging.[1-4]

An Overview of the Basic Principles

The magnetic resonance image is in certain ways analogous to the image of x-ray computed tomography. It is composed of a two-dimensional matrix of picture elements (pixels) that, when assembled together, produce a cross-section of the body (slice). Both MR and CT images are displayed in a gray scale and therefore look similar. However, the information each contains and the manner in which this information is obtained are fundamentally different.

In CT the numeric value of each pixel is determined only by the degree of x-ray attenuation in the tissue. Based on their numeric value, the individual pixels are assigned various shades of the gray scale to form a composite image of a section. The pixel values in a magnetic resonance image are determined by totally different physical properties of the tissue examined. These numeric values reflect the various intensities of a signal, which are determined principally by the number of hydrogen nuclei and their distinct behavior in disparate tissues placed in a magnetic field and subjected to repeated pulses of low-energy radio waves.

Atomic nuclei that possess an uneven number of protons or neutrons behave like tiny bar magnets when placed in a superimposed magnetic field. The hydrogen nucleus is the most ubiquitous of all such nuclei in biologic tissue and possesses the most favorable characteristics for the purposes of magnetic resonance imaging. These nuclei with their single protons are therefore the basis for producing an image.

Behavior of Hydrogen Nuclei (Protons) in a Magnetic Field

Because protons behave like magnetic dipoles when placed in an externally imposed magnetic field, given time, there is a tendency for them to line up in the direction of this superimposed field. This phenomenon can be referred to as "magnetization" of the proton sample. By disturbing this alignment of the proton sample with energy in the radiofrequency range, the rate of (re)magnetization for any particular tissue can be ascertained. This rate of magnetization is exponential and can be described by the time constant T1, referred to as "thermal" relaxation time. The term thermal comes from the fact that "thermal" collisions between molecules allow transfer of electromagnetic energy from one proton to another, a phenomenon essential to the process of magnetization. The thermal molecular environment of the protons plays a critical role in defining the value of the T1 relaxation con-

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ABBREVIATIONS USED IN TEXT
CT—computed tomography
MR—magnetic resonance

stant, and, therefore, disparate tissues can be distinguished on this basis. A second phenomenon occurs with application of the radiofrequency energy pulse to the sample of protons that are magnetized. Normally, these protons precess, or wobble, around the axis of the externally applied magnetic field. However, individual protons may have a different position in the circular route around that axis. The radiofrequency energy pulse that is applied not only changes the axis of magnetization for the ensemble of protons, but it also causes the individual protons to precess along the new axis in unison, or "in phase." When the radiofrequency excitation terminates, the protons begin to lose the unified precession or "coherence," and eventually will resume the previous axis of magnetization. During this period the nuclei will emit the added energy they had absorbed in the form of a radio wave signal. This is the signal that can be detected by sophisticated antennae used in the MR imaging instrument and subsequently encoded in the computer.

The second phenomenon described—that is, the loss of unified precession or coherence—also occurs at an exponential rate known as the relaxation time T2. The time necessary for "dephasing" of the protons' precession is dictated by local magnetic properties of the microenvironment, again a distinct physical property of a particular tissue. The initial intensity of the signal generated by the protons following their excitation by the radiofrequency pulse strongly depends on how much remagnetization had occurred (a T1 function), while the decay of this emitted signal intensity is directly due to loss of coherent precession of the nuclei (a T2 function). Clearly, the number of protons involved in the MR imaging experiment and the value of their relaxation constants T1 and T2 characterize different tissue subtypes and determine the intensity of the signal emitted from the tissue during the MR imaging process at any sampling point in time.

Varying the duration, strength and repetition rate of the applied radiofrequency pulses and the times at which the return signal is sampled permits the operator to highlight the area of interest and thus influence the signal intensity observed.

Pulse Sequences, Repetition Rates and Sampling Times

Magnetic resonance imaging techniques such as partial saturation, inversion recovery, spin-echo and saturation recovery have been popularized in the literature and refer to the sequence in which radiofrequency pulses are applied to the tissue of interest and the resultant signal sampled. As mentioned, resonating proton density, T1 and T2 relaxation values in tissue, contribute in various degrees to the final image with each of these techniques. Although the particular interplay of instrument settings and tissue characteristics and their effects on the obtained image are beyond the scope of this discussion, suffice it to say that certain techniques can highlight T1 relaxation differences in tissue and may be referred to as producing "T1-weighted" images. Conversely, other techniques sample T2 relaxation properties and produce images that can be referred to as "T2 weighted." Imaging sequences have been developed that show only proton density differences, but these do not exhibit as great a soft tissue contrast as the ones already mentioned and therefore are infrequently used clinically.

Displays of Images

The magnetic resonance study is displayed as a series of body sections. Each section may be represented by several images of distinct signal intensity patterns based on variable instrument settings designed to selectively show T1 or T2 influences. The areas of greatest signal intensity are white, the least intensity, black. Intensity is directly proportional to proton density and T2 relaxation values but inversely proportional to T1 relaxation values. Tissue with long T1 values reestablishes its original magnetization slowly and therefore emits less signal, hence the apparent inverse relationship.

Effect of Blood Flow

Rapidly flowing blood generally emits no detectable signal. The reason for this is that in the interval between application of the radiofrequency pulse and signal sampling, hydrogen nuclei in the rapidly flowing blood have a disordered pulse sequence and escape the image volume (Figure 1).[5]

Multiplanar Images

In CT the image acquisition depends on an array of x-ray tubes and detectors encircling the patient. Images can only be obtained in the plane of the machine gantry but may subsequently be reconstructed into other planes, though with loss of resolution. Magnetic resonance may image directly in any plane without the need for reconstruction, simply by reorienting the magnetic field electronically.

Figure 1.—Sagittal magnetic resonance image through the head and neck. Rapidly flowing blood in the carotid artery bifurcation (**closed arrow**) and vertebral artery (**open arrow**) results in a lack of magnetic resonance signal, resulting in their depiction as dark tubular or serpentine structures.

Characteristics of Tissue

The basis of the tissue signal or "signature" is the hydrogen nucleus, but not all hydrogen nuclei are alike. Compared with normal neural tissue, the hydrogen nuclei of pure water are very slow to remagnetize (long T1) and precess in phase for a long period (long T2). Protons in fat and in clotted blood remagnetize quickly (short T1) and also have a long T2, but not as long as pure water. Human tissues can thus be characterized by their relaxation properties (Table 1). The appearance of any particular image will therefore depend on the characteristics of the tissue and the manner in which the image was acquired (Table 2).

TABLE 1—*Characteristic T1 and T2 Values of Various Tissues Compared With Normal Neural Tissue*

	Type of Tissue	
Relative value	*T1*	*T2*
Short	Fat Blood (subacute or chronic hemorrhage)	
Intermediate	Neural tissue	Neural tissue Fat
Long	Water Cerebrospinal fluid Lesions with "increased free water content," such as tumor, infarction, infection, demyelination Blood (acute hemorrhage)	Blood (acute, subacute or chronic) Lesions with "increased free water content," such as tumor, infarction, infection, demyelination

TABLE 2.—*Relationship of Magnetic Resonance Values to Relative Image Intensity (Compared with Neural Tissue)*

	Type of Image	
Type of Tissue	*T1 Weighted*	*T2 Weighted*
Bone	No signal	No signal
Blood (acute hemorrhage)	Low	High
Blood (subacute or old hemorrhage)	High	High
Rapidly flowing blood	No signal	No signal
Fat	High	Intermediate to high
Cerebrospinal fluid	Low	Intermediate
Lesions with "increased free water content"	Low	High
Normal neural tissue	Intermediate	Intermediate

Central Nervous System—Normal Skull and Brain

The cortical bone of the skull contains little hydrogen and therefore emits essentially no signal. Fat has an intense signal so that fat present in the scalp and the marrow of the diploe results in an intense signal (white) in these areas. The brain itself is very well displayed. Gray matter contains a higher proportion of water than white matter. Thus, on T1-weighted images gray matter is less intense (darker) than the white matter. Reversal occurs on T2-weighted images. Cerebrospinal fluid has low intensity on T1-weighted images but becomes more intense on T2-weighted images.

Abnormal Brain

Initial experience has shown that most intracranial lesions characteristically have increased free water content.[6] Consequently, most lesions possess prolonged T1 and T2 relaxation values. In computed tomography the detection of a lesion depends on the difference in x-ray attenuation at the lesion compared with normal tissue. In most cases this difference is 5% or less. In contrast to CT, T1 and T2 values may differ by 100% or more between many lesions and normal brain. The MR imaging signal is based on these T1 and T2 values and thus MR imaging has superior sensitivity for most lesions.

Calcium has no magnetic resonance signal. Yet, it is recognizable if the collection is large enough by virtue of an absent signal, but punctate foci of calcification can be missed—that is, "drowned out" by the signal from the hydrogen in the immediate vicinity. CT is superior for the detection of calcium.

Tumors

MR imaging in many ways is advantageous in the imaging of neoplasms. Compared with CT, the detection rate is better,

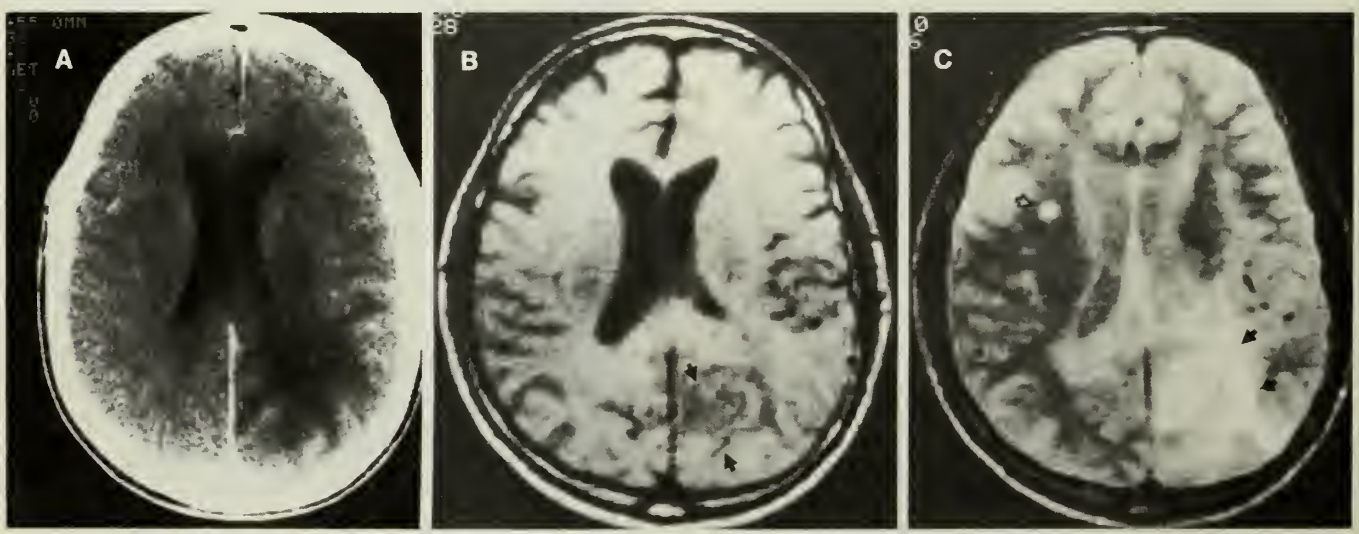

Figure 2.—Presumed left occipital glioma. **A,** A non-contrast computed tomographic (CT) scan at the level of the lateral ventricles shows an area of vasogenic edema with mass effect. **B,** A magnetic resonance study with T1 weighting shows the same low-intensity tumor (**arrows**). **C,** The edema is seen as high intensity on the T2-weighted image (**arrows**) corresponding to the edema on CT. Note second lesion in right hemispheric white matter (**open arrow**), missed with CT. (Subject's left is on viewer's right in all images.)

there is fuller appreciation of the extent of the tumor, there is broader characterization of the tissue and associated abnormalities such as hydrocephalus are more readily detected.

Generally, neoplasms are characterized by increased T1 and T2 relaxation values due to the greater free water content. Frequently there is peritumoral edema that can appear very similar to the tumor (Figure 2). The demarcation between the tumor and the edema may, therefore, be difficult to define.

MR imaging is proving to be especially useful in evaluating the posterior fossa and temporal lobes.[6-9] Both these areas are subject to troublesome artifact on CT due to their proximity to dense bone. Such artifact does not exist in MR imaging (Figure 3).

Investigators had initially hoped that quantitative analysis of T1 and T2 relaxation times would distinguish benign from malignant neoplasms. To date, most benign tumors have been found to have T1 values somewhat shorter than that of malignant lesions but there is considerable overlap.[6,10,11] Therefore, at this point it is not possible to separate these two groups.

While MR imaging is better at detecting most neoplasms, CT is currently the superior procedure for evaluating very small regions such as the pituitary gland because thinner slicing is possible. Slice thicknesses of about 7 mm have been the minimum with MR imaging and these are too large for proper imaging of the gland. Newer instruments and techniques may permit 2-mm slices.

Vascular Disease

Ischemic infarction appears as a region of high intensity on T2-weighted images due to the associated edema (Figure 4). Hemorrhagic vascular accidents appear quite distinct from ischemic ones because of the characteristic high signal intensity seen with T1-weighted images from hemorrhage, as opposed to the low signal intensity with such techniques seen in edematous regions (Figure 5).

Any intraluminal plaque can be seen as a region of relatively high signal intensity in contrast to the lack of intensity from the rapidly flowing nuclei within the blood. By extension, vascular abnormalities such as aneurysms and arteriovenous malformations are easily depicted. Their presence can be ascertained when saccular, tubular or serpiginous structures with low signal intensity are seen in the section of interest. The appearance of the saccular aneurysmal dome may be altered with the presence of stationary thrombosis within.

Infection

Cerebritis produces a nonspecific response in the brain

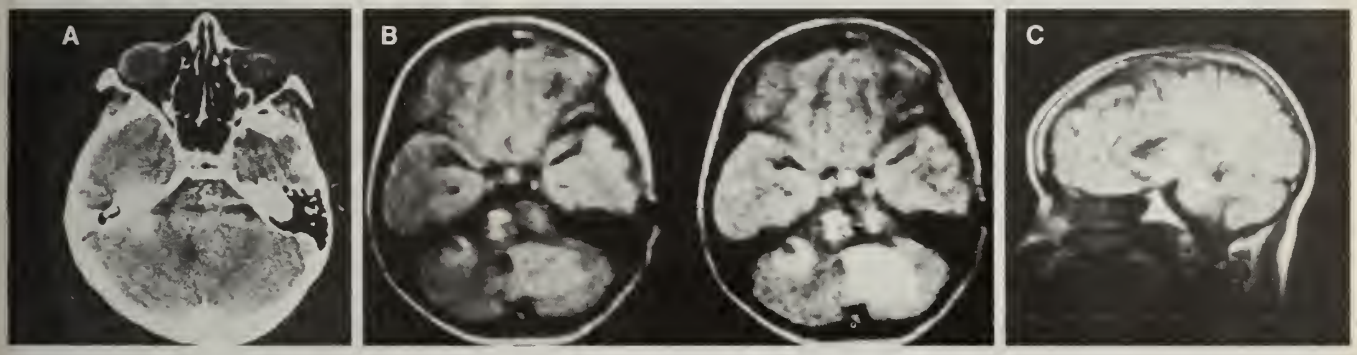

Figure 3.—Brain-stem glioma. **A,** Computed tomography (CT) depicts asymmetric enlargement of the pons, displaced fourth ventricle and an enhancing focus in the right cerebellopontile angle. There is interpetrous beam hardening artifact. **B,** A single axial section of a magnetic resonance study shows multifocal lesions on two separate samplings. The contrast is greater than with CT. The more T2-weighted image (**right**) is particularly striking. **C,** A midsagittal section depicts the glioma. (From Brant-Zawadzki et al.[6])

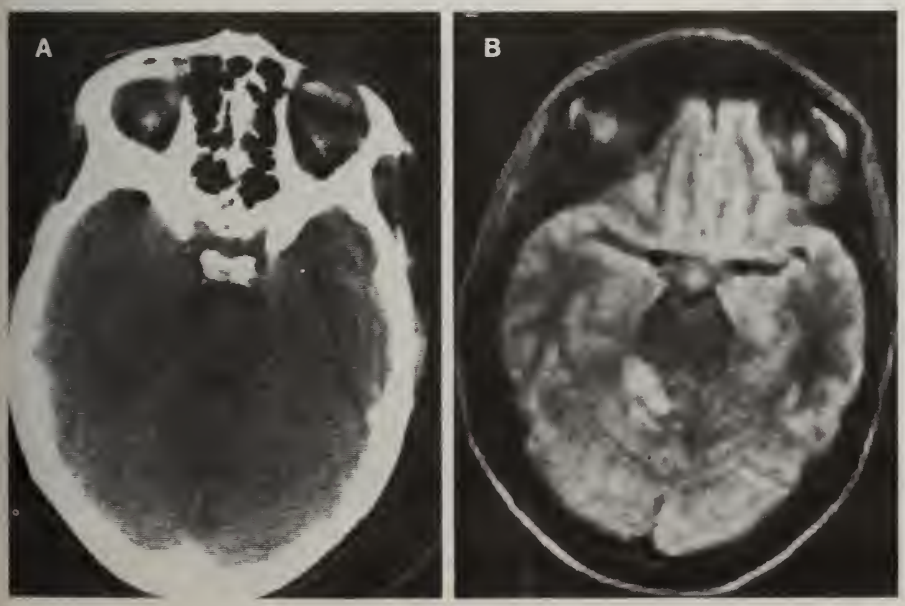

Figure 4.—Acute cerebellar infarction. **A,** A computed tomographic scan was normal in this young woman who had clinical evidence of posterior fossa emboli. **B,** A T2-weighted magnetic resonance study clearly shows one lesion in the right cerebellum 31 hours after the stroke.

that initially is represented by edema. With evolution into an abscess, a relatively necrotic, liquefied portion of the lesion is seen surrounded by edema in the border zone. The necrotic, liquefied portion of the abscess is seen as an area of low intensity on T1-weighted images, whereas the surrounding edematous brain is better defined by the high intensity signal of T2-weighted techniques. This appearance may be simulated by certain cystic neoplasms. This same problem plagues CT differentiation of the two distinct pathologic processes. Because specific histologic features are not to be expected from any imaging modality, the fundamental principle of diagnosis remains—namely, understanding the pathophysiology of disease and its expression in the context of the instrumentation used to detect it.

Demyelinating Disorders

MR imaging is exquisitely sensitive in detecting the abnormalities of white matter consequent to demyelination. Diseases such as multiple sclerosis are easily seen by virtue of the increased water content and alteration of fatty constituents that result.[12-14] They are most sensitively detected by T2-weighted techniques that show the lesions as areas of high signal intensity in a typical periventricular distribution. In a surprising number of cases, these lesions can be easily seen with MR imaging even when the CT scan is negative (Figure 6). The pronounced sensitivity of MR imaging to white matter and its myelination is of particular benefit in the pediatric population. The typical progression of myelination in an infant brain can be followed with MR imaging.[15] Disturbances of the normal pattern seen with certain disease processes can be identified.

Degenerative diseases of the gray matter, such as Wilson's disease, have also been more sensitively identified with MR imaging than with CT. The degeneration of the lenticular nucleus in Wilson's disease is evidenced by increased water content and its typical signal patterns (increased intensity on T2-weighted techniques and decreased intensity on T1-weighted techniques). However, other degenerative diseases

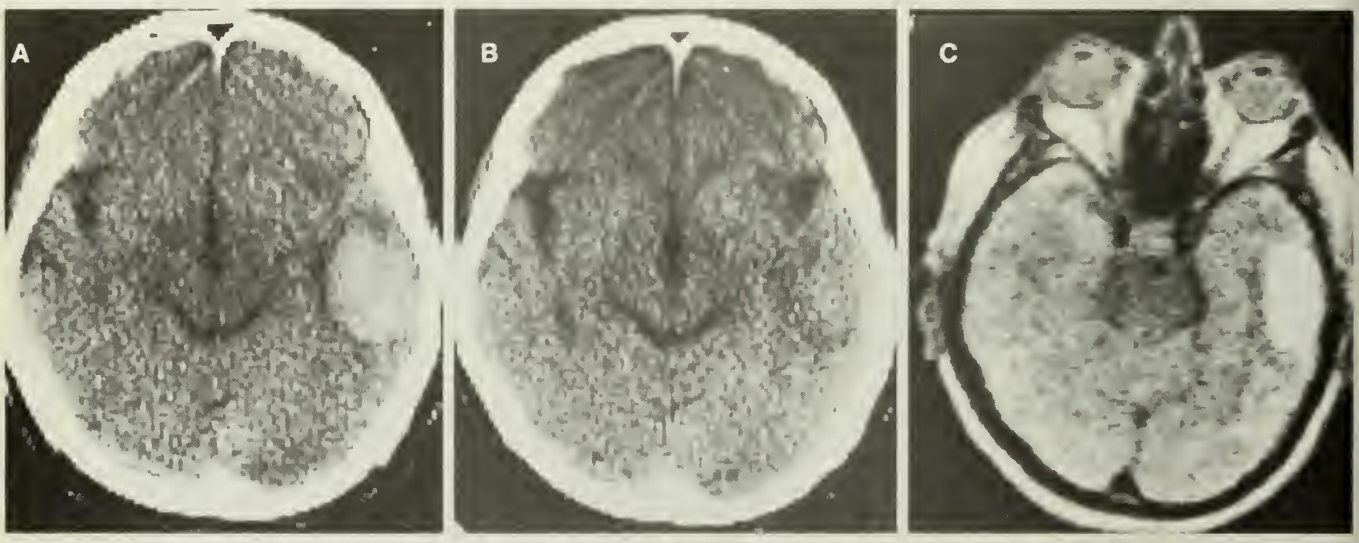

Figure 5.—Cerebral hemorrhage, with evolution. **A,** A computed tomographic (CT) scan two weeks after sudden onset of right hemiparesis in this middle-aged man shows a high-density left temporal lesion with a rim of low density. The findings are consistent with an evolving hematoma. **B,** A CT scan six weeks later shows only a vague area of residual low intensity. **C,** A T2-weighted magnetic resonance image one week after the second CT scan still shows a high-intensity focus consistent with residual hematoma. (Subject's left is on viewer's right in all images.) (From Brant-Zawadzki et al.[6])

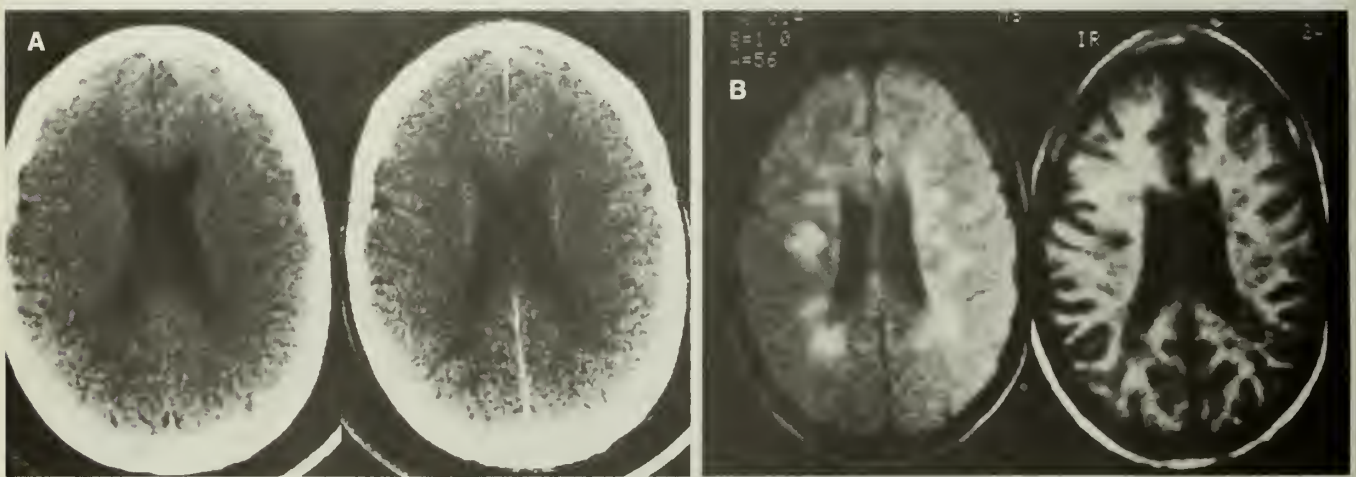

Figure 6.—Multiple sclerosis. **A,** Pre- **(left)** and post- **(right)** contrast computed tomographic scans are normal. **B,** T2-weighted **(left)** and T1-weighted **(right)** images at the same level show multiple periventricular white matter lesions, better depicted with the T2-weighted study. (From Brant-Zawadzki et al.[6])

thought to involve the gray matter, such as Alzheimer's disease and Parkinson's disease, have not shown a characteristic MR imaging appearance.

Hydrocephalus

As with CT, ventricular dilatation is easily seen. However, MR imaging allows more sensitive detection of lesions that might be the cause of such hydrocephalus (Figure 7). In addition, the presence of periventricular edema due to obstructive hydrocephalus is more sensitively identified with MR imaging than with CT.[16] The intriguing possibility that patients with hydrocephalus of long standing may be selected for shunting procedures on the basis of the presence of periventricular edema on MR imaging is now being studied.

Trauma

Patients with trauma (and other acute central nervous system insults) have not been studied in the same numbers as patients with more slowly progressing diseases. This is so because of the life-support equipment necessary for many patients who have acute disorders; such equipment cannot be brought into the MR imaging suite with its powerful magnetic fields. However, the small number of patients with intracerebral and extracerebral hematomas studied to date has shown that such lesions are more sensitively detected with MR imaging than with CT. Extracerebral hematomas can be especially difficult to detect with CT and their presence occasionally is inferred indirectly by their mass effect. This is especially the case with small, or bilateral, isodense subdural hematomas. MR imaging has been successful in detecting such lesions regardless of their size, radiographic density or bilaterality.[17,18]

Hairline skull fractures may not be detected by MR imaging, but larger fractures, or displaced ones, should be easily seen because of the signal from the blood or tissue in the fracture line.

Spinal Imaging

Normal Spine and Spinal Cord

The cortical bone of the vertebral column is of low intensity. Marrow, because of its fat and blood contents, can be easily detected within the spinal column. Within the disc spaces, the nucleus pulposus can be easily seen because of high signal intensity and is surrounded by the relatively low-signal-intensity annulus fibrosus. The subarachnoid cerebrospinal fluid is low in signal intensity, except with techniques using strong T2 weighting. The spinal cord is of uniform, intermediate intensity and stands out in sharp contrast against

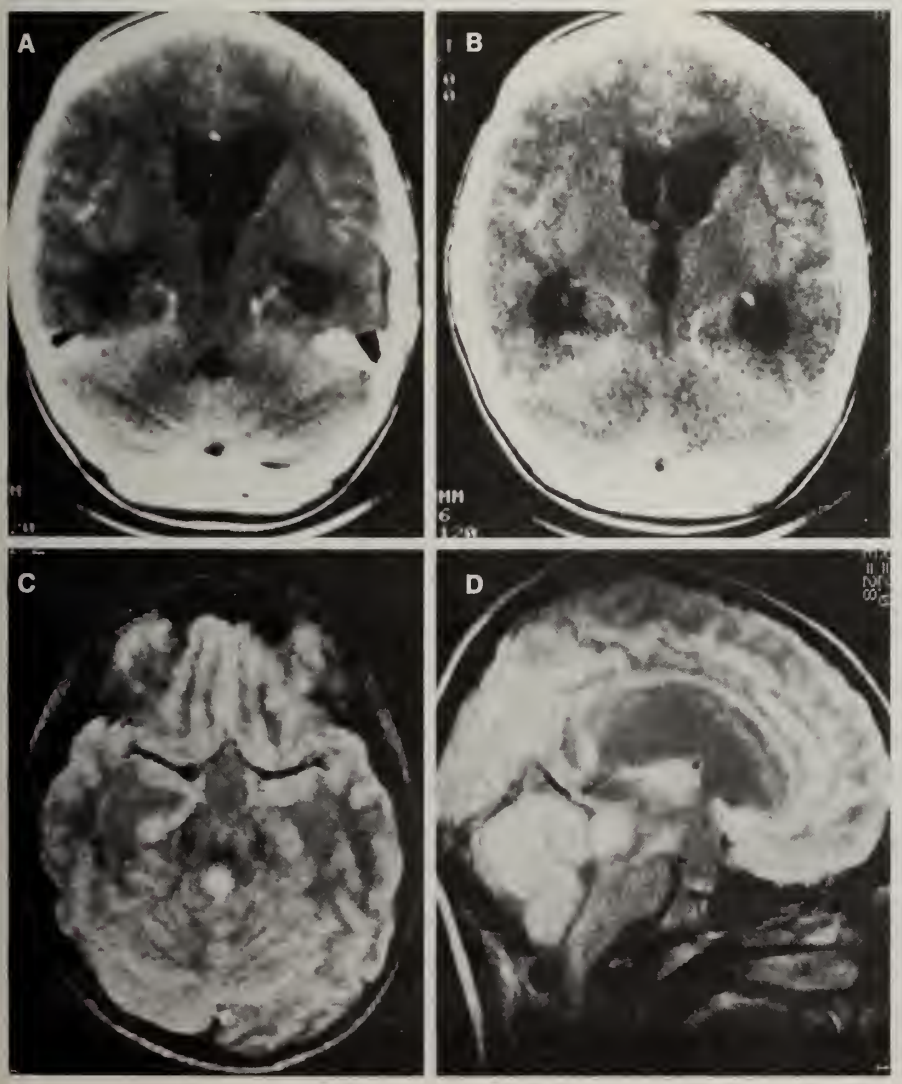

Figure 7.—Obstructive hydrocephalus due to midbrain glioma in a patient with neurofibromatosis. **A** and **B**, Computed tomographic scans at the level of the third ventricle **(A)** and the midbrain **(B)** show dilated ventricles but no obstructing lesion was seen. A provisional diagnosis of aqueductal stenosis was made, a known association with this disorder. **C**, An axial T2-weighted magnetic resonance study clearly shows a high-intensity midbrain lesion. **D**, A midline sagittal section shows the same lesion, which was a midbrain glioma.

the low intensity of the cerebrospinal fluid on T1-weighted techniques. To date, differentiation of gray versus white matter in the spinal cord has not been successful with MR imaging, presumably due to partial volume averaging difficulties associated with relatively thick sections.

Sagittal images are best at showing the cord over 10 to 12 vertebral segments and offer superb display of anatomy without the use of any intrathecal contrast agents.

Abnormal Spine and Spinal Cord

The appearance of hemorrhage, fat, neoplastic tissue, edema and cerebrospinal fluid is very similar to that discussed within the intracranial region. Specific lesions within the spinal region will be discussed briefly.

Degenerative disease. Degeneration of the nucleus pulposus can be directly visualized. Degenerated discs show relative loss of water content and appear as lesser intensity structures than adjacent normal discs, especially on T2-weighted images (Figure 8).[19] Herniation of the nucleus can be shown by its interface with the cerebrospinal fluid. This is best detected on T2-weighted techniques where the cerebrospinal fluid space, showing relatively high signal intensity, is displaced by the disc material of low intensity.

Figure 8—Degenerated intervertebral disc. The discs at the L3-4 and L4-5 interspaces are normal and appear as high intensity structures. The disc at L5-S1 is abnormally low in intensity, indicating loss of normal hydration (arrow).

Difficulty in evaluating patients with low back pain by MR imaging may be encountered due to the fact that degenerative bony spurring is a common feature of this disease process and such spurs are difficult to identify sensitively with MR imaging. Because bone produces high x-ray attenuation values, CT is more effective at showing hypertrophic spur formation. Nevertheless, the impingement of such a process on a cerebrospinal fluid-filled thecal sac or spinal cord can be delineated with MR imaging.

Syrinx. MR imaging has proved very useful in detecting and delineating the extent of syringomyelia and hydromyelia. Associated ectopia of cerebellar tonsils can also be directly visualized without the need for exogenous contrast agents (Figure 9). Posttraumatic syringomyelia and syringobulbia are easily seen. These cystic collections within the spinal cord behave like relatively pure liquid and show low signal intensity versus the surrounding neural tissue. In view of this, MR imaging has already been shown to be the procedure of choice to demonstrate the Chiari malformation.

Tumors. Expansion of the spinal cord by tumor is difficult to distinguish from the expansion associated with intramedullary cavities on conventional imaging techniques. However, the MR signal characteristics of tumor differ considerably from those discussed with syringomyelia. This is especially well shown with T2-weighted images, where tumors exhibit high intensity characteristics. The extent of the tumor can be easily determined with sagittal imaging.[20,21] The reliability of distinguishing benign from malignant neoplasms within the cord has not been determined.

Demyelinating disease. The plaques of multiple sclerosis may affect the spinal cord in the same manner that they affect the brain. However, the relatively small anteroposterior diameter of the cord and the currently relatively thick sections used make such plaques difficult to detect at the present time. It is hoped that with advancements in instrumentation design, the ability to diagnose intramedullary demyelinating plaque will be improved.

Limitations of MR Imaging

Despite the above discussion with its emphasis on the advantages of MR imaging, certain problems still exist with this imaging method. Patients with cardiac pacemakers, intracranial aneurysm clips, large metal joint prostheses or life-support equipment cannot currently be imaged with this new method.[22-24] In fact, patients with pacemakers should not approach any area where the magnetic field may exceed 5 gauss. The risk to a patient is that the rapidly changing magnetic fields may induce currents in the pacemaker leads and interfere with normal pacemaker function. Close proximity to the large static magnetic field may cause positional changes of the pacemaker in the chest, clearly an unwelcome event.[23]

Aneurysm clips containing paramagnetic material undergo torque when in the magnetic field, leading to the possible risk of dislodgement.[22,25] Risk can be reduced by the appropriate selection of alloys for future manufacture of these clips.

Even though large joint prostheses probably will not present a significant risk, caution is currently exercised, as in one in vitro study there was a 5° C temperature rise when two large prostheses were in contact in a saline buffer.[22] Such a situation is unlikely to occur in humans but further evaluation

is required to study such patients with MR imaging. It should be mentioned parenthetically that more than 1,000 patients have been studied so far at the University of California at San Francisco without any apparent adverse effect occurring.

Other Hazards

Magnetic objects in proximity to the magnet may, if large enough, be drawn into the field, becoming hazardous projectiles. Because of this, should medical intervention be required during such a study, such as with cardiac arrest and resuscitation, the patient must be removed from the imaging room.

Artifacts

Movement still produces artifacts with MR imaging, though the artifacts are not as significant as in CT imaging. Metallic objects within tissue produce gross streak artifacts on CT, but such objects produce only a local artifact on MR images, which does not detract from the rest of the section of interest.

Imaging and Duration of Examination

Magnetic resonance imaging will only replace computed tomography if it proves to be not only more informative, but equally efficient. This challenge has been met in the evaluation of the central nervous system, as pulse sequences have been defined that optimally screen for the presence of disease. A complete study of the brain or spinal cord using a multislice technique currently requires between 13 and 17 minutes, producing 20 consecutive sections centered 10 mm apart. Imaging in an additional plane requires a repeated sequence, as does characterization of any lesion detected with a separate technique aimed at T1 weighting. In general, a patient evaluation takes less than half an hour, which is comparable to CT when a similar volume of tissue is studied.

Contrast Agents

The absence of the need to intravenously administer contrast agents with MR imaging has been lauded as one of its major advantages compared with CT. However, certain instances may require the use of agents that change the local magnetic environments of tissues. Such substances can help enhance areas of tissue abnormality, may allow the "tagging" of specific tissue with monoclonal antibodies and produce even more tissue characterization capability than is currently inherent in the MR imaging instruments. In addition, paramagnetic contrast agents may allow further evaluation of normal tissue function, organ perfusion and other aspects of physiology currently undetermined.[26,27]

Summary

As we have seen above, the attractive aspects of magnetic resonance imaging are the superior ability in detecting disease, the improved ability to characterize such processes, the direct multiplanar capability of this imaging modality and the

Figure 9.—Tonsillar ectopia in a patient with Arnold-Chiari I malformation. The fourth ventricle is low in position. The tonsils **(closed arrows)** extend below the level of the foramen magnum **(open arrows).**

lack of significant biologic hazards. Limitations of the technique include the relatively thick sections currently available compared with CT, the slightly longer patient examination time compared with CT, insensitivity to calcium and the need to exclude certain patients because of magnetic materials and life-support systems. Nevertheless, the accumulated experience to date has already suggested that MR imaging is the preferred modality when screening patients for the presence of disease in the central nervous system. The degree to which this method becomes successful will, in part, be influenced by the current medical economic climate. Nevertheless, the benefits to patients have already been shown. It is difficult to imagine that the major and unprecedented benefits this procedure offers could be negated by economic considerations. The cost-benefit analysis of this new imaging technique must await further experience and the inclusion of other organs besides the central nervous system. Without question, the influence of MR imaging in the field of medicine will be much more profound in the years to come.

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Specialty Conference

Polyamines in Clinical Disorders

Moderator
DONALD F. TIERNEY, MD

Discussants
LAURENCE J. MARTON, MD; ALLEN D. HACKER, DrPH, *and* NICHOLAS LOWE, MD, MRCP

An edited summary of an Interdepartmental Conference arranged by the Department of Medicine of the UCLA School of Medicine, Los Angeles. The Director of Conferences is William M. Pardridge, MD, Associate Professor of Medicine.

Polyamines, necessary for cell growth, influence many cell functions. As small polyvalent cations they can change the configuration of large polyvalent anions, such as DNA, and alter their sensitivity to other molecules including chemotherapeutic agents. By altering polyamine content in a cell, we can change its growth, its susceptibility to drugs and change other cellular functions. Malignant conditions, other proliferative diseases and infections are the most apparent clinical conditions likely to improve by depleting polyamines and suppressing cell growth. Proliferative disorders of the skin respond to many agents that suppress polyamine metabolism. Hyperoxia may suppress cell growth in the lung by suppressing polyamine metabolism.

(Tierney DF, Marton LJ, Hacker AD, et al: Polyamines in clinical disorders—Interdepartmental Conference, University of California, Los Angeles [Specialty Conference]. West J Med 1985 Jan; 142:63-73)

DONALD F. TIERNEY, MD:* Polyamines promote cell growth. Although this statement is correct, it does not project the anticipation by investigators that cell growth may be controllable by manipulating polyamine metabolism nor does it describe the many other roles of polyamines. Perhaps a clue to their importance is their presence in nearly all living cells; their contents change remarkably rapidly during the cell cycle.

Whether with normal or abnormal cell growth, the polyamines play critically important roles.[1-4] They also influence cell differentiation,[3] immune responses[5,6] and secretory processes.[7,8] They stabilize membranes,[2] oppose oxidants,[9] scavenge free radicals,[10] promote protein, RNA and DNA synthesis and probably have many other biologic functions. Although some of these roles have been recognized for many years, few interventions seemed clinically useful until a brilliant application of enzyme theory led to synthesis of a remarkable inhibitor of polyamine metabolism, difluoromethylornithine.[11] The conference discussants will describe some of its uses.

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The most apparent clinical interest in polyamines is to suppress growth of tumors or infections; there is also, however, great potential usefulness for polyamines in other proliferative states, such as psoriasis, or the normal repair with cell growth that occurs after tissue injury.

Despite their complex roles, polyamines have simple structures and readily identified crystals. About 300 years ago Leeuwenhoek described typical polyamine crystals in semen, and during the next two centuries similar crystals (Charcot-Leyden and Böttcher's crystals) were recognized in other body secretions and tissues.[2] The two major polyamines (spermidine and spermine), and the related diamine putrescine, were isolated and identified more than a half century ago. Polyamines were recognized 35 years ago as growth promoters for microbes and 20 years ago as growth factors for mammalian cells in culture.[2] The development of more sensitive methods to analyze tissues rapidly for polyamines have enabled investigators to relate polyamines to physiologic conditions; newly developed inhibitors of polyamine metabolism made it possible to observe the effects of polyamine deprivation. During the past 20 years interest in polyamine metabolism entered a logarithmic growth phase.

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ABBREVIATIONS USED IN TEXT

AdoMet DC = *S*-adenosylmethionine decarboxylase
BCNU = 1,3-bis (2-chloroethyl)-1-nitrosourea
MGBG = methylglyoxal-bis(guanylhydrazone)
TPA = tetradecanoyl-phorbol-13-acetate

Figure 1 shows the interrelations between the polyamines and enzymes discussed in this paper. Structures of the diamines and polyamines are very simple; they are chains of carbon and nitrogen atoms. Polyamines are derived from the amino acid ornithine, which is not incorporated into polypeptides or proteins and therefore has limited incorporation into other metabolites. Decarboxylation by ornithine decarboxylase produces the diamine putrescine; two amino groups are separated by four carbons. To form the polyamines spermidine and spermine, one or two propylamine groups must be added to putrescine. The source of propylamine groups depends on the enzyme *S*-adenosylmethionine decarboxylase (AdoMet DC), which is the second enzyme of polyamine metabolism that has been widely studied. These simple molecules are among the few organic polycations in mammalian cells, and their role in stabilizing complex molecules, as well as membranes, probably relates to their capacity to bridge between anionic sites such as phosphate groups in DNA.

All subspecialties of internal medicine will find potentially important applications of polyamine metabolism. Nephrologists will be interested in the possible roles of polyamines in the kidney with acute injury and the reports that elevated spermine content may be responsible for the anemia associated with uremia[12]; gastroenterologists will note the possible roles of polyamines in regulating gastric secretion as well as their potential role in cell growth to repair ulcers and other diseases of the gut[13]; cardiologists should ponder the pronounced and prompt (two-hour) changes of ornithine decarboxylase that occur when isoproterenol is given to isolated perfused rat hearts and the suppression of that response reported to occur with hyperoxia.[14,15] Hematologists will find several potential roles for polyamines including their capacity to act as free radical scavengers.[9,10] As Dr Marton will discuss, oncologists have perhaps the most apparent reasons to be interested in polyamines as growth factors within malignant cells; immunologists may find that the current evidence linking polyamines with the immune process may be of significant value in many clinical conditions.[5,6] Those interested in infectious diseases should be pleased with one of the first successful clinical applications of polyamine antagonists—treating trypanosomiasis[16]—and their potential for treating other infections.[17]

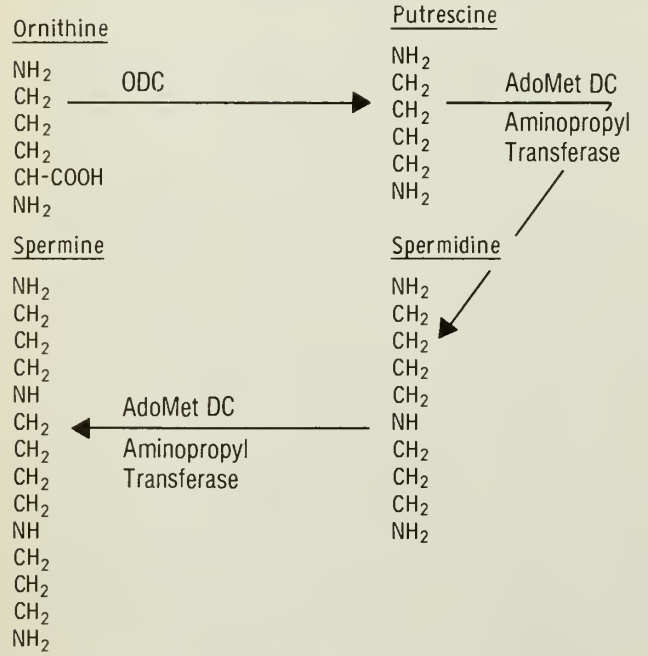

Figure 1.—This diagram indicates most of the enzymes and polyamines discussed. *S*-adenosylmethionine decarboxylase provides the aminopropyl group that is transferred to putrescine or spermidine as indicated. ODC = ornithine decarboxylase; AdoMet DC = *S*-adenosylmethionine decarboxylase.

Dr Laurence Marton will describe the clinical usefulness of an understanding of polyamine metabolism when treating cancer; Dr Allen Hacker will relate polyamines to the suppression of cell growth that occurs transiently with hyperoxia and to the subsequent cell growth during the repair of lung injury, and Dr Nicholas Lowe will discuss proliferative disease of the skin.

Polyamines and Cancer Therapy

LAURENCE J. MARTON, MD:* Although the complexities of the growth of normal and malignant cells are not well understood, it is apparent that polyamines are intimately involved with the growth process.[18] All mammalian cell systems that initiate growth in vitro or in vivo do so with a concomitant increase in the activity of the rate-limiting polyamine biosynthetic enzymes and in the intracellular concentrations of the polyamines. Even though it is not known whether polyamine accumulation regulates initiation of cell growth or whether, once initiated, cells require polyamines to maintain growth, it is now clear that if polyamine biosynthesis is interrupted, growth will cease.[19] Because neoplastic cells usually grow more rapidly and contain higher intracellular concentrations of polyamines than their counterpart normal cells, manipulation of polyamine biosynthesis in neoplastic cells is an obvious approach to cancer therapy. Inhibitors of polyamine biosynthesis have been synthesized and studied as tools with which to probe polyamine function and as agents with which to explore the potential of polyamine biosynthesis modulation as a therapeutic modality.

The concept of using highly cytotoxic drugs to destroy cancer cells is well understood and has been used clinically for many years; other—perhaps in comparison, subtle—approaches to cancer therapy, however, are less well understood and only recently have been studied as possible alternatives to traditional therapy. The use of relatively nontoxic drugs to retard or to prevent tumor repopulation during the interval between courses of cytocidal therapy is one approach. Another is the use of one agent to potentiate the cytocidal effect of a second agent without significantly increasing toxicity to normal tissues. We have reported possible advantages of these approaches.[20] Inhibitors of polyamine biosynthesis not only have the potential of acting as cytocidal agents, but some, such as α-difluoromethylornithine (a compound that is easily

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administered, relatively nontoxic, inhibits cell proliferation and potentiates the cytotoxicity of other chemotherapeutic agents), have the necessary characteristics to be useful in the latter two approaches.

A variety of compounds that inhibit polyamine biosynthesis, primarily by interfering with ornithine decarboxylase or AdoMet DC, have been synthesized. Methylglyoxal-bis(guanylhydrazone) (MGBG) is an extensively studied competitive inhibitor of AdoMet DC that effectively blocks the formation of the polyamines spermidine and spermine. Cytotoxic effects of MGBG, however, may not be related entirely to inhibition of polyamine biosynthesis.[19] Clinical trials of MGBG are currently being conducted. Several ornithine decarboxylase inhibitors that have different modes of action have been synthesized and studied.[19]

The actions of α-difluoromethylornithine, an enzyme-activated, irreversible inhibitor of ornithine decarboxylase, have been studied extensively in vitro and in vivo and this drug is now in clinical trial. This compound usually depletes cells of putrescine and spermidine with little or no effect on levels of spermine. It is cytotoxic against human small cell carcinoma,[21] rat 9L tumor spheroids[22] and murine B16 melanoma.[23] However, in virtually all other models in which α-difluoromethylornithine has been studied, little or no cytotoxicity has been found, even though growth is inhibited or halted.

Neither α-difluoromethylornithine nor MGBG depletes cells of polyamines totally. It is likely that a specific inhibitor or a combination of inhibitors that could deplete cells of all polyamines would be cytotoxic. In addition to synthesizing new inhibitors of ornithine decarboxylase and AdoMet DC, compounds that may inhibit the spermidine and spermine synthases are being synthesized[24]; when available, these inhibitors will be studied either alone or in combination with other inhibitors in attempts to induce either more specific or more complete depletion of polyamines. Polyamine analogues may not only inhibit biosynthesis, but may compete with cellular polyamines for binding sites that have specific biologic functions.

Methylglyoxal-bis(guanylhydrazone) is a spermidine analogue, the toxicity of which may be in part related to such competition. Other polyamine analogues that either may act directly or may be converted through polyamine biosynthetic pathways into polyamine analogues that are unable to function biologically are being synthesized.[25]

Among the many cellular functions described for the polyamines, their ability to interact with and stabilize cellular DNA is well documented.[26–30] Recently we have shown that the conformation of DNA from 9L rat brain tumor cells depleted of polyamines with α-difluoromethylornithine is changed compared with the conformation of DNA from untreated cells.[31] Thus, the positions of, or the accessibility to, DNA reactive sites with which drugs react may be changed in space. We postulated that polyamine depletion might alter the reaction between various chemotherapeutic agents and DNA and thereby modify the cytotoxic actions of these agents.

The chloroethylnitrosourea, 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU), is thought to kill cells by alkylation and cross-linking of DNA.[32] We have shown that treatment of monolayer 9L cells[33] or of 9L multicellular spheroids[22] with α-difluoromethylornithine to deplete polyamine levels before BCNU treatment potentiates the cytotoxicity of BCNU. However, because BCNU can carbamoylate, monoalkylate and cross-link DNA, we were uncertain which of these biochemical reactions was modified by polyamine depletion. In studies conducted with nitrosoureas that primarily carbamoylate, alkylate or cross-link DNA, we found that polyamine depletion had no effect on cytotoxicity caused by monoalkylating agents, inhibited the cytotoxicity caused by a carbamoylating agent and potentiated the cytotoxicity caused by the cross-linking agent.[34] Using alkaline elution techniques to measure directly DNA cross-link formation, we have shown that DNA cross-links caused by BCNU are increased in 9L cells depleted of polyamines by treatment with α-difluoromethylornithine.[35] These data support the idea that polyamine depletion can alter chemosensitivity by altering reactions between drugs and DNA. In addition, damage to chromosomes caused by BCNU and measured with the sister chromatid exchange assay is also increased in 9L cells depleted of polyamines by treatment with α-difluoromethylornithine.[36] All of the effects described can be prevented if exogenous putrescine is added to culture medium to restore intracellular polyamine levels.

Using the murine glioma 26 and the 9L rat intracerebral tumors in vivo, we investigated the ability of α-difluoromethylornithine to delay tumor repopulation and to potentiate BCNU cytotoxicity by treating animals with α-difluoromethylornithine either before or after a single dose of BCNU.[37] In our experiments, either approach significantly prolonged survival.

We have shown that in 9L cells pretreated with α-difluoromethylornithine, the cytotoxicity of *cis*-diamminedichloroplatinum (II) (cisplatin), another chemotherapeutic agent that cross-links DNA, although somewhat differently than BCNU, was decreased[38] and that damage to chromosomes[36] and the amount of DNA cross-linking[35] were likewise decreased compared with effects in 9L cells treated with cisplatin alone. Addition of exogenous putrescine prevents all of these effects. Thus, polyamine depletion alters chemosensitivity of two cross-linking agents differently, potentiating one and inhibiting the other.

There are reasonable molecular mechanisms to help explain the different effects that polyamine depletion has on the cytotoxic effects caused by BCNU and cisplatin. After the initial metalation reaction, cisplatin is confined to forming a cross-link across the 0.33-nm distance that separates its reactive groups; thus, any change in the spatial separation or orientation of DNA nucleophiles, which are normally 0.34 nm apart, will decrease the possibility of forming cisplatin cross-links. In contrast, treatment of cells with BCNU produces chloroethyl-DNA alkylation products; the chloroethyl group is more flexible than the DNA-platinum complex and a conformational change in DNA may favor the displacement reaction on the chloroethyl group that forms the cross-link. Another possible explanation is that BCNU may cross-link DNA across areas that are occupied normally by polyamines; thus, when polyamines have been depleted, cross-linking is favored. It is important both in terms of molecular biologic mechanisms and therapeutic effect to consider that, despite the fact that the change in DNA conformation caused by polyamine depletion is the same, the effects on the reactions between DNA and drugs, and thus on cytotoxicity, are agent-de-

pendent, and may confer a therapeutic advantage with some agents but may be therapeutically detrimental with other agents.

Mechanisms that do not directly involve DNA, which account for the polyamine depletion-induced modification of the cytotoxic effects of chemotherapeutic agents, have also been described. Sunkara and associates[39] have shown that HeLa cells treated with α-difluoromethylornithine accumulate in the S phase of the cell cycle and are killed more effectively by cytarabine (cytosine arabinoside), an S-phase-specific agent, than HeLa cells treated with cytarabine alone. Rupniak and Paul[40] and Sunkara and co-workers[41] showed that a variety of "normal" cell lines accumulated in G_1 phase when treated with polyamine biosynthesis inhibitors, while various transformed cells accumulated in S-phase after the same treatment. This result suggests the possibility that pretreatment with an inhibitor of polyamine biosynthesis should protect normal tissues from S-phase-specific agents and should increase the relative cell kill of tumor cells caused by the same S-phase-specific agents. However, we have shown that pretreatment of 9L cells with α-difluoromethylornithine dramatically inhibited the cytotoxicity of cytarabine.[42] Although 9L is a transformed line, flow cytometric analysis showed that α-difluoromethylornithine treatment did not cause 9L cells to accumulate in S-phase.[43] Different results obtained by treatment with the same combination of agents in different models emphasize the need to investigate the response of several cell lines, particularly if cell cycle effects are presumed to be involved, before conclusions about possible clinical use are made.

Methylglyoxal-bis(guanylhydrazone) competes with the polyamines for cellular uptake via a facilitated transport mechanism. Pretreatment of both experimental[44] and human[45] tumors with α-difluoromethylornithine increases MGBG uptake, which is the result of the creation of a large concentration gradient when polyamines are depleted intracellularly and there is a significant amount of MGBG present extracellularly.[44] Several clinical trials designed to investigate the use of this approach are under way. Because MGBG is a relatively toxic agent, this approach should have clinical use only if the uptake of MGBG is greater in tumor than in normal cells.

The activity of interferon against B16 melanoma can be greatly potentiated by α-difluoromethylornithine[23]; the effects of hyperthermia against Chinese hamster ovary cells can be potentiated by pretreatment with either α-difluoromethylornithine or MGBG.[46] Although the mechanisms that lead to these effects are still not known, the potential clinical use of these findings must be considered.

Polyamine biosynthesis inhibitors used in combination protocols should be given in the correct sequence and at the correct doses. It is essential to maximize tumor cell kill or cytostasis and to minimize toxicity. Consideration must be given to the fact that polyamine biosynthesis inhibitors not only decrease the growth of tumors but also affect rapidly growing normal tissues. For instance, gastrointestinal and hematologic toxicities, which are usually relatively mild and reversible, have been reported to occur secondary to α-difluoromethylornithine treatment. In addition, it has been shown that, although α-difluoromethylornithine does not affect the gastrointestinal tract of normal adult rats, α-difluoromethylornithine administered after the gastrointestinal tract has been injured with cytarabine delays the repopulation of the gastrointestinal mucosa.[13]

Because of the increasing interest in polyamine biosynthesis inhibition both for the study of basic biochemical phenomena and for clinical use, a variety of new agents are becoming available that inhibit polyamine biosynthetic enzymes more efficiently, that inhibit other enzymes in the biosynthetic pathway and that possibly interfere with polyamine function because they are polyamine analogues. Because of the diverse ways these agents may act on cells, laboratory studies are needed before clinical trials can be initiated. These studies will not only expand our knowledge of the polyamines but of the mechanism of action of various therapeutic modalities.

Polyamine Metabolism of Lungs and Oxygen Toxicity

ALLEN D. HACKER, DRPH:* For good recovery immediately following acute lung injury, such as the adult respiratory distress syndrome, cell growth must be controlled, or interstitial pneumonitis or pulmonary fibrosis may develop. Oxygen toxicity, a model of adult respiratory distress syndrome in rats, has been used to study acute lung injury and the repair processes that follow. Our interests are in the suppression of cell growth caused by oxygen and in the capacity for repair through cell proliferation, both of which may relate to the phenomenon of "tolerance."

Oxygen tolerance is "decreased sensitivity to 1 atm of oxygen." For example, when 60-day-old (300- to 350-gram) rats are moved directly from air into 1 atm oxygen, they die within 72 hours; but when other 60-day-old rats are first exposed to 0.85 atm oxygen and then placed in 1 atm oxygen,[47] they survive for several weeks. This change in sensitivity to oxygen toxicity has been called "tolerance," and it may be important when humans are given high concentrations of oxygen for several days.

Oxygen tolerance in rats is associated with cellular injury and with a repair process involving a tremendous increase in cell proliferation.[48] Because cell proliferation replaces injured epithelial and endothelial cells, it may affect survival during the first seven days of adult respiratory distress syndrome. Using oxygen toxicity as a model of adult respiratory distress syndrome, investigators have found several stages in rats similar to those reported for humans.[49] When animals are exposed to 0.85 to 1.0 atm oxygen, severe injury occurs during the first three days: they become sluggish and barely move in their cages. The loss of endothelial cells is greatest by 60 hours[48] and is accompanied by huge pleural effusions. However, if the rats survive to the fifth day, they become more active, the pleural effusions decrease in volume and the lungs begin to have evidence of mitosis. The rat lung adapts to the injury in some manner.

On the other hand, oxygen is one of many agents that suppress cell growth and interfere with polyamine metabolism. Although rat lung cells proliferate by five days in 0.85 atm oxygen,[50] hyperoxia initially suppresses cell proliferation. Oxygen between 0.3 and 1.0 atm inhibits DNA synthesis and cell division in cultured cells for up to four days[51]

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and 1.0 atm oxygen suppresses ^3H thymidine labeling of mouse lung cells below control values for at least 48 hours.[52] We found that ornithine decarboxylase activity increased an additional twofold two days after rats were removed from 17 days of exposure to oxygen (seven days in 0.85 atm and ten days in 1.0 atm oxygen, unpublished observations, September 1981), which is consistent with a sudden escape from suppression.

There is evidence that hyperoxia suppresses cardiac ornithine decarboxylase activity by oxidizing essential sulfhydryl groups[15]; the reported suppression of cell proliferation by hyperoxia[51] might, therefore, be related to suppression of polyamine metabolism. Oxygen toxicity associated with increased superoxide production might decrease putrescine production by attacking ornithine decarboxylase. Such an effect could limit cell growth in the injured lung because putrescine seems to be essential for liver growth after partial hepatectomy.[53] However, we exposed 60-day-old rats to 0.85 atm oxygen and did not find such an effect of hyperoxia on lung ornithine decarboxylase, which increased notably during oxygen toxicity (Figure 2).[50] Even greater increases might have occurred if sulfhydryl groups had not been attacked. We also found an increase in putrescine after exposure to 0.85 atm oxygen (Figure 3).[50] Hyperoxia did not suppress DNA synthesis by suppressing ornithine decarboxylase as we had postulated from the reports of heart ornithine decarboxylase activity.[14]

Another possible mechanism by which hyperoxia may suppress polyamine metabolism is through AdoMet DC activity, which can be inhibited by products of lipid peroxidation.[54] Could oxygen suppress cell growth by preventing an

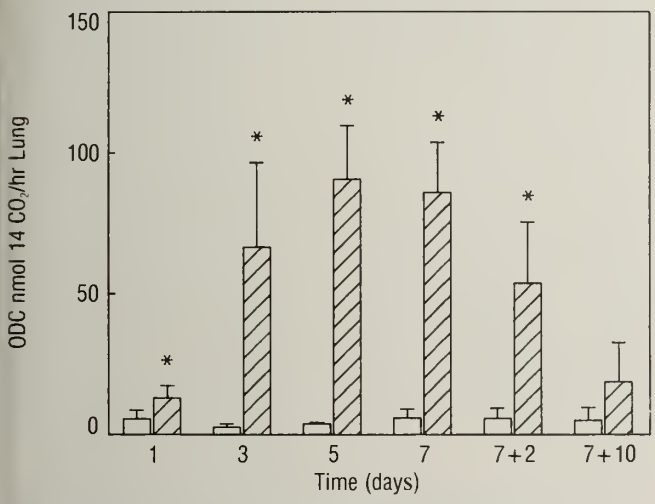

Figure 2.—Ornithine decarboxylase (ODC) activity in 60-day-old rat lung during oxygen exposure (0.85 atm O_2 for seven days followed by 1.0 atm O_2 for ten days). Statistical significance ($P < .05$), N = 5. (From Hacker et al.[50] By permission of *Biochemical and Biophysical Research Communications.)* Clear bars represent air-exposed lungs; stippled bars represent oxygen-exposed lungs.

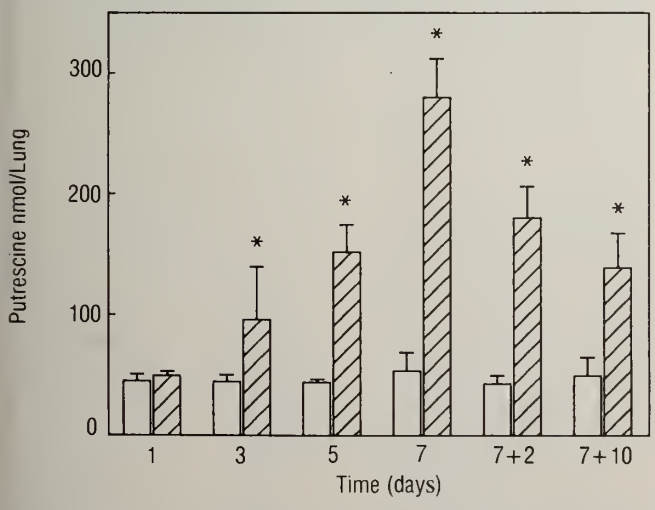

Figure 3.—Effects of oxygen exposure on putrescine in 60-day-old rat lung (0.85 atm O_2 for seven days followed by 1.0 atm for ten days). Statistical significance ($P < .05$), N = 5. (From Hacker et al.[50] By permission of *Biochemical and Biophysical Research Communications.)* Clear bars represent air-exposed lungs; stippled bars represent oxygen-exposed lungs.

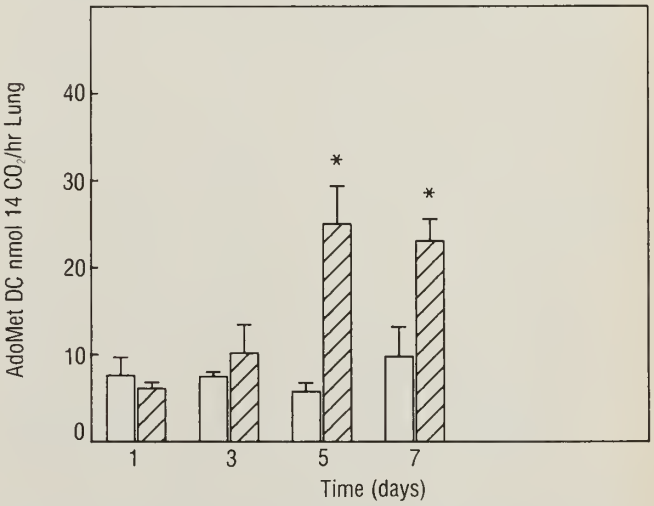

Figure 4.—Effects of oxygen exposure on *S*-adenosylmethionine decarboxylase (AdoMet DC) activity in 60-day-old rat lung (0.85 atm O_2 for seven days followed by 1.0 atm for ten days). Statistical significance ($P < .05$), N = 5. (From Hacker et al.[50] By permission of *Biochemical and Biophysical Research Communications.)* Clear bars represent air-exposed lungs; stippled bars represent oxygen-exposed lungs.

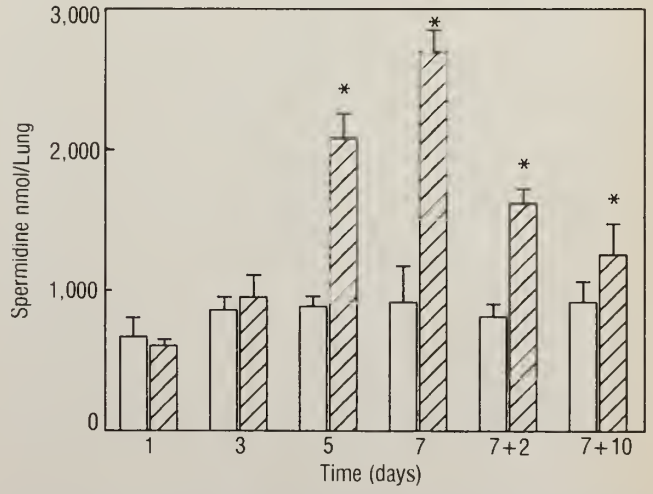

Figure 5.—Effects of oxygen exposure on spermidine activity in 60-day-old rat lung (0.85 atm O_2 for seven days followed by 1.0 atm for ten days). Statistical significance ($P < .05$), N = 5. (From Hacker et al.[50] By permission of *Biochemical and Biophysical Research Communications.)* Clear bars represent air-exposed lungs; stippled bars represent oxygen-exposed lungs.

increase in the activity of AdoMet DC? In nearly all reports, this activity increased within 12 hours of ornithine decarboxylase activity.[55] With hyperoxia, however, ornithine decarboxylase activity increased within one day but AdoMet DC activity did not increase until after three days (Figure 4).[50] As expected, the delayed increase in AdoMet DC activity was associated with delayed increases in spermidine (Figure 5)[50] and spermine (Figure 6).[50] To test the possibility that lung tissue generally has such delayed increases in AdoMet DC activity we exposed rats to ozone (unpublished observations, June 1983): the lung immediately became injured and AdoMet DC activity increased within two days. The results with 0.85 atm oxygen are consistent with the reported suppression of AdoMet DC activity by products released during lipid peroxidation.[54]

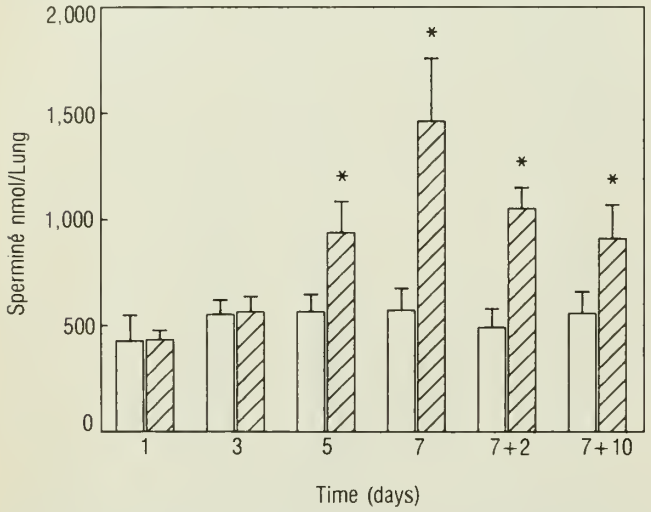

Figure 6.—Effects of oxygen exposure on spermine in 60-day-old rat lung (0.85 atm O_2 for seven days followed by 1.0 atm for ten days) Statistical significance ($P < .05$), N = 5. (From Hacker et al.[50] By permission of *Biochemical and Biophysical Research Communications.*) Clear bars represent air-exposed lungs; stippled bars represent oxygen-exposed lungs.

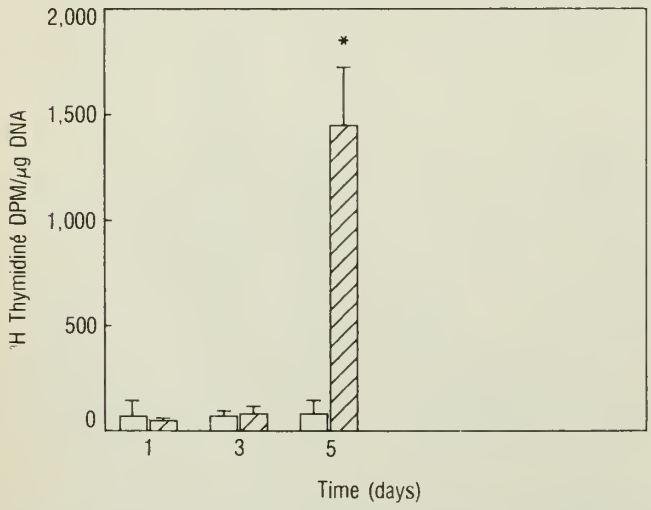

Figure 7.—Tritiated thymidine incorporation into lung DNA during oxygen exposure (0.85 atm O_2 for five days; rats were 60 days old). Statistical significance ($P < .05$), N = 5. (From Hacker et al.[50] By permission of *Biochemical and Biophysical Communications.) Clear bars represent air-exposed lungs; stippled bars represent oxygen-exposed lungs. DPM = disintegrations per minute*

Our data using tritiated thymidine incorporation (Figure 7)[50] indicate that DNA synthesis increases at about five days, the same time interval for increases of AdoMet DC activity, spermidine and spermine content. Any delayed increases of AdoMet DC activity would delay increases of spermidine and spermine, which seem to be required for maximal DNA synthesis.[56]

These observations may relate to oxygen "tolerance." We postulate that prolonged "tolerance" requires cell growth and, in response to injury from oxygen (0.85 atm), there is an increase in polyamine metabolism, which is required for increased DNA synthesis and in turn for increased cell proliferation. This increased cell proliferation is needed to repair the ongoing injury associated with prolonged exposure to 1.0 atm oxygen.

Tolerance to oxygen toxicity seems to depend on various factors. Recent reports have examined changes in protective enzymes, such as superoxide dismutase, catalase and glutathione peroxidase. Several laboratories have shown[47,48,57]

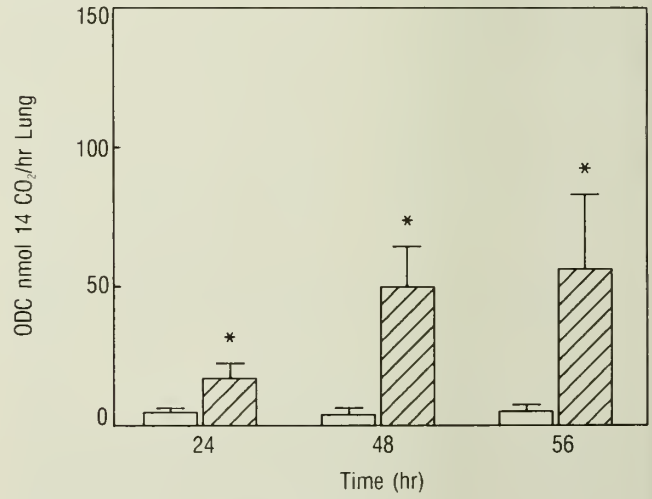

Figure 8.—Ornithine decarboxylase (ODC) activity in rat lung during oxygen exposure (1.0 atm O_2 for 56 hours; rats were 60 days old). Statistical significance ($P < .05$), N = 5. Clear bars represent air-exposed lungs; stippled bars represent oxygen-exposed lungs.

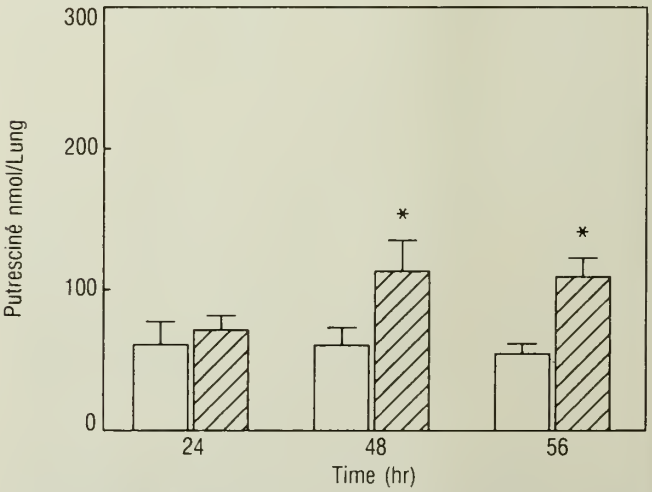

Figure 9.—Putrescine content in rat lung during oxygen exposure (1.0 atm O_2 for 56 hours; rats were 60 days old). Statistical significance ($P < .05$), N = 5. Clear bars represent air-exposed lungs; stippled bars represent oxygen-exposed lungs.

that the development of tolerance is accompanied by an increase in the activities of these protective enzymes, which could reduce lung injury by removing the toxic substances. We propose that an additional factor is the rapid repair of injury, but increased spermidine and spermine content might also assist in removing toxic substances.[58]

To test the hypothesis that increases in polyamine metabolism are associated with tolerance, we exposed 60-day-old rats to 1.0 atm oxygen for up to 56 hours and compared changes in polyamine metabolism with those in similar rats that had been exposed previously to 0.85 atm oxygen for seven days. We found that exposure of 60-day-old rats to 1.0 atm oxygen for 48 hours resulted in increases in ornithine decarboxylase activity (Figure 8) and putrescine content (Figure 9) but no increases of AdoMet DC activity were detected nor did spermidine or spermine contents increase (unpublished observations, May 1982). Furthermore, DNA synthesis as reflected by the incorporation of tritiated thymidine (unpublished observation, May 1982) did not increase. In contrast, "tolerant" rats that had been exposed to 0.85 atm oxygen already had elevated polyamines before they were placed in 1.0 atm oxygen (Figures 3, 5 and 6). Consequently, after 48 hours of subsequent exposure to 1.0 atm oxygen, these values were already elevated and presumably the cells in the lung had an increased capacity for cell growth. These rats survived continuous exposure for at least ten days ((Figures 3, 5 and 6). Our data, therefore, suggest a correlation between increases in polyamine metabolism and the prolonged survival of 60-day-old rats in 1.0 atm oxygen. The evidence for decreasing polyamine metabolism after prolonged exposure may be related to decreasing injury as other enzymes protect the lung from toxic substances.

Sensitivity to oxygen is known to vary with age, but the mechanism to explain this phenomenon is unknown. In contrast with 60-day-old rats, 30-day-old rats become tolerant and are able to survive exposure to 1.0 atm oxygen for several weeks.[59] Autor and colleagues[60] have reported that protective enzymes such as superoxide dismutase may be induced more quickly in younger rats. Superoxide dismutase[61] and the glutathione peroxidase system[47] might contribute to this tolerance.[47,57] Another possibility is that cells may proliferate more quickly in young rats and replace injured cells. We therefore evaluated the possibility that differences in polyamine metabolism and DNA synthesis might be detectable, which would indicate possible differences in cell growth between younger and older rats. In 30-day-old rats, ornithine decarboxylase activity and putrescine content increased as for 60-day-old rats, but there were also increases in AdoMet DC activity, spermidine content and in the incorporation of tritiated thymidine into lung DNA (unpublished observations, April 1983). Changes in AdoMet DC, spermidine and tritiated thymidine did not occur immediately after increases of ornithine decarboxylase activity and putrescine content; these changes, therefore, were delayed in a manner similar to that observed for 60-day-old rats after exposure to 0.85 atm oxygen.

The response to oxygen toxicity varies between different species of animals. Several laboratories have reported great differences between rats and mice in survival and in adaptation of the lung to hyperoxia. Light microscopy shows that the two species have similar abnormal changes during the first three days of exposure; however, superoxide dismutase, glucose-6-phosphate dehydrogenase and glutathione peroxidase activity in mouse lung does not increase after three days of exposure as it does in rats.[47,49,57,61] Furthermore, rats, after an initial lung injury that increases the activity of these enzymes, can survive 20 to 40 days in 1.0 atm oxygen, whereas such "tolerance" does not develop in mice. The differences between these species have been used to support the postulate that "tolerance" is related to increased activities of these enzymes.[47,59-61]

Similarly, we tested the possibility that changes in polyamine metabolism and DNA synthesis were different between these species, which, if true, would confirm our postulate. Evans and co-workers[52,62] reported that the Swiss-Webster mouse lung when exposed to 40%, 60% and 80% oxygen had a decrease in DNA synthesis until the fifth day and then returned to normal. They did not find a burst in DNA synthesis (such as the 18-fold increase we found in rats [Figure 7]). Although hyperoxia suppresses DNA synthesis,[51] the rat lung overcomes that inhibition by the fifth day at 0.85 atm oxygen when the mouse lung does not seem to show such a change. From our studies with rats it seems that the delayed increase of AdoMet DC activity and spermidine content correlates with DNA synthesis. We have found that 0.85 atm oxygen does increase ornithine decarboxylase activity in mouse lung (unpublished observation, August 1981) but we have not yet determined when AdoMet DC activity or spermidine and spermine contents change.

To test the hypothesis that polyamines play an important role during lung injury and the subsequent repair, we attempted to suppress DNA synthesis by depleting lungs of polyamines using antimetabolites, such as α-difluoromethylornithine and dicyclohexylamine. Pösö and Pegg[53] reported suppression of DNA synthesis in the liver by giving high doses of α-difluoromethylornithine that blocked putrescine production after partial hepatectomy in the rat. Dicyclohexylamine inhibits bacterial[17] and mammalian[63,64] spermidine synthase and suppresses growth of some experimental tumors.[17]

In a preliminary study (unpublished observations, January 1983) we gave 60-day-old rats dicyclohexylamine (170 mg per kg body weight per day, using an Alzet osmotic pump) and α-difluoromethylornithine (2% in drinking water) either separately or combined (dicyclohexylamine, 170 mg per kg a day, using an Alzet osmotic pump plus α-difluoromethylornithine, 330 mg per kg a day, using an Alzet osmotic pump) during exposure to 0.85 atm oxygen or filtered air for seven days. No deaths (0/2 in oxygen) occurred in the dicyclohexylamine group, six deaths (6/10 in oxygen) occurred in the α-difluoromethylornithine group in 0.85 atm oxygen, and five deaths (5/5 in oxygen) in the group given both dicyclohexylamine and α-difluoromethylornithine in 0.85 atm oxygen. Death occurred in the rats between days four and five, which is the time when spermidine and spermine increase in other rats. Our results suggest that increases in polyamines are related to the ability of rats to survive in oxygen.

We have assumed that DNA synthesis can be impaired by depleting the lung of polyamines during oxygen toxicity. However, polyamines may have other important roles[1-3,65-68] in RNA and protein synthesis and in cell differentiation. The death of animals receiving polyamine antimetabolites may,

therefore, be attributed to the role of polyamines in cell functions other than those relating to DNA synthesis. If we can suppress cell proliferation without severely injuring the cells by using antimetabolites of polyamines, we will be able to test whether the increased metabolic activity of protective systems (superoxide dismutase, glutathione peroxidase) requires cell proliferation and whether cell proliferation may be required for prolonged survival even with the increased protective mechanisms. The results may have clinical significance because many patients in respiratory care units have received chemotherapy for malignant lesions or other drugs that may suppress cell proliferation. By understanding some of the mechanisms by which oxygen injures the lung and the cellular repair processes, we hope eventually to be able to generalize the function of polyamines to other conditions.

Polyamine Abnormalities in the Skin

NICHOLAS LOWE, MD:* In 1976 O'Brien[69] suggested that epidermal ornithine decarboxylase induction is a critical component of the expression of a tumor phenotype that is produced by certain phorbol ester tumor-promoting agents. He also proposed that a tumor initiator may delete the gene responsible for controlling ornithine decarboxylase activity, so that ornithine decarboxylase activity greatly increases in the initiated cells after promoter treatment. O'Brien and associates[70] found that a single topical application of the tumor promoter, tetradecanoyl-phorbol-13-acetate (TPA), resulted in a rapid transient increase in mouse epidermal ornithine decarboxylase activity. These changes occurred much sooner than any subsequent increase in epidermal DNA synthesis. The stimulation of AdoMet DC was less pronounced. These workers also showed that the induction of epidermal ornithine decarboxylase was largely prevented by pretreatment of mouse skin with cycloheximide and azacytidine. They suggested that specific messenger RNAs are synthesized and that translation resulted in increased ornithine decarboxylase activity.

Important work on the effects of all-*trans*-retinoic acid on the tumor-promoting ability of TPA has also been published. Verma and Boutwell[71] reported that the application of retinoic acid to mouse skin before application of TPA produced a dramatic reduction in the level of ornithine decarboxylase activity induced in the epidermis by TPA. In contrast, treatment with all-*trans*-retinoic acid did not significantly suppress AdoMet DC activity induced by TPA. In a further series of experiments, the application of all-*trans*-retinoic acid before the application of TPA substantially reduced the number of papillomas produced per mouse. Application of retinoic acid at various times in relation to the time of initiation with dimethylbenzanthracene did not alter the incidence of skin papillomas. Thus, it seems that all-*trans*-retinoic acid inhibited the induction of epidermal ornithine decarboxylase activity by TPA and that it also reduced the frequency of skin papillomas formed by TPA promotion. These workers suggested that the inhibition of epidermal ornithine decarboxylase activity induced by TPA may be a useful assay for screening anti-tumor-promoting properties of retinoids.

Anti-inflammatory agents can affect the induction of epidermal ornithine decarboxylase activity by tumor promoters. Epidermal ornithine decarboxylase activity induced by TPA is inhibited by prior treatment with indomethacin[72] and anti-inflammatory corticosteroids (fluocinolone acetonide and fluocinonide) can inhibit tumor promotion when applied to mouse epidermis.[73]

The effect of ultraviolet irradiation on epidermal ornithine decarboxylase activity has been studied recently[74] because of the association of polyamine biosynthesis with tumor promotion and cellular hyperplasia. Ultraviolet light, a potent carcinogen, also produces epidermal hyperplasia.

Irradiation of hairless mice with ultraviolet light mainly in the sunburn range (ultraviolet-B—290 to 320 nm) results in a dramatic increase in epidermal ornithine decarboxylase activity as early as two hours after ultraviolet-B exposure. Maximum activity occurred about 28 hours after treatment. Thereafter, ornithine decarboxylase activity declined, returning to original levels 47 hours after ultraviolet-B irradiation. The ultraviolet-B irradiation also led to increased activity of AdoMet DC.

Incorporation of tritium thymidine into epidermal DNA was initially depressed, but a fourfold increase occurred 48 hours after ultraviolet-B exposure. Histologic examination of ultraviolet-B-treated skin showed considerable epidermal thickening within 48 hours.

The role of ultraviolet irradiation as a major causal factor of human skin cancer is well documented. Evidence from animal studies indicates that ultraviolet-B is the most carcinogenic region of the ultraviolet spectrum. Exposure to ultraviolet-B radiation results in epidermal cell death, an increased mitotic index, erythema, an acceleration of macromolecular synthesis and accumulation of vasoactive substances such as prostaglandins.[75]

Topical triamcinolone acetonide and indomethacin were found to significantly inhibit the induction of epidermal ornithine decarboxylase in hairless mice when applied after ultraviolet-B irradiation. Triamcinolone also inhibited the accelerated DNA synthesis after ultraviolet-B irradiation but indomethacin did not.[75]

Greaves and Sondergaard[75] first reported prostaglandin-like activity in perfusates from human skin that had been irradiated with ultraviolet rays. There may, however, be mechanisms for the inhibition of TPA-induced ornithine decarboxylase activity[76] by indomethacin other than prostaglandin synthetase inhibition.

The controversy over whether topical all-*trans*-retinoic acid enhances or inhibits ultraviolet carcinogenesis remains unresolved. Application of retinoic acid enhances the carcinogenic ability of ultraviolet light and Epstein[77] originally reported that 0.3% all-*trans*-retinoic acid applied to mouse skin in conjunction with ultraviolet light increased the carcinogenic effect. More recently, however, it was found that other concentrations of all-*trans*-retinoic acid did not enhance ultraviolet light carcinogenesis and may have decreased it.[78]

We studied the effects of all-*trans*-retinoic acid on ultraviolet-B-induced ornithine decarboxylase activity in concentrations that are capable of inhibiting TPA-induced ornithine decarboxylase activity. All-*trans*-retinoic acid was applied in 0.1 ml acetone to the skin of hairless mice either an hour before or immediately after exposure to ultraviolet-B light. We found that a single application of all-*trans*-retinoic acid inhibited ornithine decarboxylase induction when the mice

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were sacrificed six hours after ultraviolet-B irradiation, but not at 24 hours. Five applications each hour of all-*trans*-retinoic, either before or after ultraviolet-B irradiation, inhibited 6-hour and 24-hour ornithine decarboxylase induction.

The ability of retinoids to partially inhibit ultraviolet-B-induced epidermal ornithine decarboxylase is of interest but the mechanism is unknown. The mechanism may be important, however, because we have found that similar treatment regimens of all-*trans*-retinoic acid have a modulating effect on ultraviolet-B carcinogenesis.[79]

Polyamine Abnormalities in Psoriatic Skin

Polyamine concentrations are elevated during states of rapid cellular proliferation[23,80] and in both involved and uninvolved psoriatic skin, epidermal cells proliferate more rapidly than in normal skin.[81,82] Polyamine metabolism in cases of psoriasis has been reported previously to be abnormal; the concentration of spermine and spermidine was particularly increased in the blood of patients with psoriasis,[83] and ornithine decarboxylase activity was significantly higher in psoriatic skin than in normal skin.[84] Levels of putrescine, spermine and spermidine are notably higher in both involved and uninvolved psoriatic skin when compared with normal skin.[84] Further study of uninvolved psoriatic skin showed that spermine and spermidine concentrations were normal, but the putrescine level was greater. In the same study, putrescine, spermine and spermidine concentrations were significantly elevated in involved psoriatic skin; dithranol treatment reduced the polyamine concentrations in involved skin towards normal.[85]

We have studied cutaneous polyamines in psoriasis in an attempt to characterize the patterns of polyamine abnormalities in this disease (Table 1)[86] and their potential modulation by a retinoid.[87] Epidermal shave biopsy specimens were taken from the gluteal skin of patients with psoriasis and from normal volunteers. The uninvolved skin of patients with psoriasis was taken from an area at least 5 cm from any neighboring psoriatic lesion. The samples were frozen in liquid nitrogen within 10 seconds of removal and then stored at −70° C until processed. A representative section of each biopsy specimen was examined microscopically and only those samples containing full-thickness epidermis with minimal dermal contamination were analyzed for polyamines. None of the patients had been treated within the previous two weeks.

Part of each sample was assayed for ornithine decarboxylase activity after homogenization. The rest of the sample was assayed for polyamine content using a Durrum D500 amino acid analyzer. The concentrations of putrescine were greater in involved psoriasis skin, but they did not substantially differ from uninvolved and involved psoriasis skin. Concentrations of spermine and spermidine were greater in both involved and noninvolved psoriatic skin compared with normal, and the spermine-to-spermidine ratio was increased in involved skin compared with uninvolved and normal skin. The ornithine decarboxylase activity in involved skin was elevated compared with uninvolved and it was also elevated in the uninvolved skin of patients with psoriasis when compared with normal skin.[86]

In these studies we confirmed abnormalities of putrescine content and ornithine decarboxylase activity in involved skin of patients with psoriasis, but we did not find notable differences of putrescine content of uninvolved skin compared with that of normal skin. This may suggest insufficient epidermal hyperplasia in uninvolved skin to produce measurable elevations of putrescine content. A previous study of psoriasis also showed ornithine decarboxylase activity to be increased, but not statistically different, between uninvolved and normal skin.[84]

Of potential significance are the findings that spermine and spermidine concentrations are both elevated in involved and uninvolved epidermis. Previous studies suggested that an elevated spermine-to-spermidine ratio might be related to hyperproliferative states; we found this feature in involved skin of our patients with psoriasis.[86]

A recent clinical study of different possible therapeutic agents in psoriasis included an inhibitor of AdoMet DC activity, MGBG, which improved psoriasis.[88] MGBG inhibits spermidine formation and DNA synthesis in lymphocytes stimulated to proliferate by mitogens. Further studies with psoriatic skin should determine spermine and spermidine content as well as expand our knowledge of putrescine content, and ornithine decarboxylase and AdoMet DC activity, in psoriasis.

Polyamine Modulation by Retinoid Therapy in Psoriasis

Because previous studies of the polyamines and their rate-limiting biosynthetic enzyme have shown significant increases in psoriasis and because retinoids are known to modulate polyamine biosynthesis in several other situations,[71,89] we measured epidermal ornithine decarboxylase acitivity and polyamine content before and after one month's treatment with an aromatic retinoid, etretinate (0.6 mg per kg of body weight), of patients with severe psoriasis. No topical therapy was permitted during this month. After etretinate treatment, epidermal ornithine decarboxylase activities were still elevated compared with those of normal skin but had fallen

TABLE 1.—*Levels of Putrescine, Spermidine and Spermine in Epidermal Shave Biopsy Specimens**†

Polyamines	*Involved Psoriasis N = 9*	*Uninvolved Psoriasis N = 9*	*Normal N = 4*
Putrescine	2.17 ± 1.54‡	0.46 ± 0.70§	0.86 ± 0.25
Spermidine	17.7 ± 10.9‡	21.3 ± 6.9‡	1.77 ± 0.41
Spermine	16.7 ± 11.8‡	35.6 ± 7.2‡	2.17 ± 0.53
Spermidine/spermine ratio	1.09 ± 0.19‡	0.59 ± 0.9§	0.86 ± 0.34

*From Lowe et al.[86]
†nmol/mg protein ± standard deviation.
‡$P < .05$ (or less) compared with normal.
§$P > .05$ (not significant) compared with normal.

substantially and were similar in involved and uninvolved psoriasis skin. Thus, the degree of inhibition of ornithine decarboxylase activity was greatest in involved skin.[87]

It is unlikely that cutaneous polyamine abnormalities represent a primary defect in psoriatic skin because such differences have been noted in several other situations of epidermal hyperplasia. Polyamines, however, may be important cell regulatory factors in psoriasis, and modulation of polyamine biosynthesis may be an important effect of therapy. An example may be the inhibitory effects of etretinate on ornithine decarboxylase activity in our patients.

Retinoids Inhibit Polyamine Biosynthesis in Experimental Benign Epidermal Hyperproliferation

One method of producing benign epidermal hyperproliferation and rapid ornithine decarboxylase induction is to strip the stratum corneum of a hairless mouse with adhesive tape.[90] Ten consecutive tape strippings result in considerable ornithine decarboxylase induction four hours after the stripping. We found that different retinoids varied in their ability to inhibit the induction of ornithine decarboxylase activity in this situation in a dose-dependent manner.[90] Inhibition of the induction of ornithine decarboxylase may be useful to evaluate new retinoids for their therapeutic effects.

Further studies of cutaneous polyamines may advance knowledge of the stages of skin carcinogenesis and be useful to study modulators or protectants of cutaneous carcinogenesis. Epidermal polyamine assays might also be used to study possible antiproliferative agents useful for the treatment of psoriasis.

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Controversies in the Medical Management of Stroke

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs Homer A. Boushey, Associate Professor of Medicine, and David G. Warnock, Associate Professor of Medicine, under the direction of Dr Lloyd H. Smith, Jr, Professor of Medicine and Chair of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

DR SMITH:* *One of the neglected areas in internal medicine is that of cerebrovascular accidents. A patient with a stroke is often considered to be on the frontier between medicine and neurology, with neither discipline directing the attention to this group of patients that the seriousness of the illness warrants. For this Medical Staff Conference, Dr Michael E. Charness from the Department of Neurology will discuss this topic for us.*

DR CHARNESS:† I would like to examine some currently controversial areas in the medical management of patients with stroke, with an emphasis on the still-confusing issue of anticoagulation.[1] I will focus on the role and timing of anticoagulation in cases of cardiac embolic stroke, stroke in evolution, transient ischemic attacks (TIAs) and completed stroke. I will not deal extensively with the overall medical and surgical management of cases of TIA, which have been reviewed recently.[2]

Cardiac-Cerebral Embolism

Cardiac-cerebral embolism is increasingly recognized as an important cause of stroke. Thirty years ago, emboli arising from the heart were felt to account for just 3% of all strokes; in current series, with better diagnosis of predisposing cardiac conditions, this estimate has risen to around 20%.[3] For the purpose of this discussion, the term "embolic stroke" will refer to strokes caused by nonseptic emboli arising from the heart but not from the carotid artery.

The diagnosis of cardiac-cerebral embolism is largely clinical. In most patients a sudden neurologic deficit develops that is maximal at onset. Transient ischemic attacks precede few of these strokes.[4] The carotid circulation of the brain, which receives the highest percentage of cerebral blood flow, is affected in most cases; hence, in most patients a mixed sensorimotor deficit will develop, accompanied at times by aphasia and homonymous hemianopia. Seizures accompany between 10% and 15% of cases of embolic stroke and less than 3% of cases of nonembolic ischemic cerebral infarction. Clinical or radiologic evidence of infarction in several cerebrovascular territories and computed tomographic (CT) evidence of hemorrhagic infarction, while uncommon, are highly indicative of embolic stroke or vasculitis.

The "smoking gun" that most implicates the heart in cerebral infarction is, of course, the presence of an appropriate predisposing cardiac lesion. In Table 1 are summarized many of the presently recognized cardiac lesions associated with embolic stroke.[3] Arrhythmias, including atrial fibrillation of both ischemic and rheumatic causes, are especially important. Embolization after myocardial infarction generally occurs within six weeks and is more likely with large infarcts, transseptal infarcts, ventricular aneurysms or accompanying congestive heart failure.[3,4] Mitral valve prolapse has been identified in 40% of stroke patients younger than age 45; however, stroke in this age group is itself relatively uncommon.[5]

Anticoagulation is of unquestionable benefit in a variety of disorders associated with embolization from the heart or veins. However, the prompt use of anticoagulation for cardiac-cerebral embolism has been restrained by certain clinical concerns. That is, 44 years ago, Fisher and Adams found microscopic petechial hemorrhage dotting the region of cerebral infarction in numerous autopsy specimens from cases of embolic stroke.[4] There has therefore been legitimate concern that prompt anticoagulation could harm patients who have cardiac-cerebral embolism by converting an ischemic infarct into a hemorrhagic infarct. Four considerations dominate this area of controversy: (1) the risk of recurrent embolization after an initial embolic stroke, (2) the timing of recurrence, (3) the efficacy of anticoagulation in preventing both short-term and long-term recurrences and (4) the risks of anticoagulation. The information governing these issues is less complete than one would hope. Nevertheless, I will

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ABBREVIATIONS USED IN TEXT
CT = computed tomography
TIA = transient ischemic attack

briefly synthesize the available data, with suggestions for patient management.

Risk and Timing of Recurrent Cerebral Embolism

Older studies, based largely on patients with rheumatic heart disease, indicate that among patients with an initial cerebral embolism, about 40% will have a recurrent event within ten years, most of these within six months.[4] Darling and co-workers found an equal risk of recurrence among patients who had rheumatic heart disease or nonrheumatic atrial fibrillation and following myocardial infarction.[6] In several recent studies, cerebral embolism recurred within just one to two weeks of an initial cardiac embolic event in between 10% and 20% of patients.[7-10] Hence, patients with cardiac-cerebral embolism of various causes have a significant (10% to 20%) risk of recurrent embolism within a short (7 to 14 days) period of time.

Efficacy of Anticoagulation in Preventing Recurrent Embolism

The efficacy of anticoagulation in preventing cerebral embolism must also be discerned mostly from older, suboptimal clinical studies. Anticoagulation with sodium warfarin appears to reduce the long-term risk of recurrent embolization by as much as 80% to 90%.[3,11] This benefit has been best shown for patients with rheumatic heart disease, but appears likely for patients with nonrheumatic atrial fibrillation and in patients after a myocardial infarction.

The effect of prompt anticoagulation on early recurrent cerebral embolism has been the subject of a number of recent nonprospective investigations. For cases of cardiac-cerebral embolism of various causes, anticoagulation within 48 hours reduced the incidence of reembolization during the subsequent two weeks from 13% to less than 5%.[7-10] A randomized prospective study found similar results, though the number of patients and events was small.[10]

Anticoagulation, therefore, appears to be effective in preventing late recurrent embolism due to cardiac disease and, when begun promptly, may also reduce the early risk of recurrent embolic stroke.

Risk of Anticoagulation in Patients With Cardiac-Cerebral Embolism

The next area of controversy concerns the risk of anticoagulation in patients with cardiac-cerebral embolism. Whether or not effective in reducing the risk of early recurrent embolism, prompt anticoagulation could be justified only if the benefits outweighed the risks. Of special concern is the potential for immediate anticoagulation to cause clinically significant intracerebral hemorrhage.

Although microscopic hemorrhage is frequently identified in postmortem specimens from cases of embolic stroke, CT evidence of macroscopic hemorrhage during life is actually quite rare. Hart and colleagues, in a retrospective study, found CT evidence of hemorrhagic infarction in just 4/147 (3%) patients with embolic stroke.[12] Koller and associates reported similar results.[7]

Furlan and co-workers prospectively examined the brain CT scan of 54 consecutive patients with cardiac-cerebral embolism, including 35 patients who had a second CT scan after adequate anticoagulation was achieved.[8] They found CT evidence of hemorrhage in just one (2%) patient. Although heparin therapy was continued in this patient, there was no subsequent deterioration either clinically or radiographically. Reembolization occurred in 5/25 (20%) patients in whom anticoagulation was delayed by more than 24 hours and in 0/23 patients who were anticoagulated within 24 hours.

The possible benefit and the safety of prompt anticoagulation were recently evaluated in a prospective cooperative study.[10] Anticoagulation was carried out safely in 24 patients with embolic stroke; in fact, hemorrhagic transformation of lesions occurred in only two patients, neither of whom had been anticoagulated. The risk of hemorrhagic infarction appeared to be related to the size of the initial embolic infarction. Early recurrent embolic stroke occurred only among nonanticoagulated patients. This study, which showed a trend toward reduction of early recurrent embolic stroke by heparin, was unfortunately terminated before statistical significance could be determined.

The overall safety of continuous intravenous heparin therapy was examined in 510 patients with strokes of different causes.[13] The risk of central nervous system hemorrhage was only 0.8%. In all, five deaths were associated with hemorrhagic complications of therapy. Heparin therapy had to be discontinued in 3.1% due to overt systemic hemorrhage,

TABLE 1.—*Cardiac Lesions Producing Cerebral Embolic Events* *

Cardiac Condition	*Nature of Embolus*
Myocardial infarction	Mural thrombi
Postinfarction aneurysms and akinetic segments	Stasis thrombi
Postinfarction atrial fibrillation	Atrial thrombi
Mitral stenosis with or without fibrillation	Atrial or auricular thrombi
Atrial fibrillation of any cause	Atrial thrombi
Mitral regurgitation with atrial mural 'jet lesions'	Small mural thrombi
Bacterial endocarditis	Valvular mycotic thrombi
Nonbacterial thrombotic endocarditis	Valvular thrombi
Prolapsing mitral valve	Valvular thrombi, atrial thrombi
Mitral annulus calcification	(?) Degenerate valve fragments
Calcific aortic stenosis	(?) Degenerate valve fragments
Atrial myxoma	Neoplastic fragments, (?) attached thrombi
Prosthetic heart valve	Attached thrombi

*From Barnett et al.[3]

1.8% due to occult hemorrhage and 1.4% due to heparin-associated thrombocytopenia. The major risk for systemic hemorrhage was age 60 years or older. Intracerebral hemorrhage complicated heparin therapy in 2 of 152 patients with a known cardiac source for embolization. While infrequent overall, intracerebral hemorrhage occurred more often in patients with large cerebral infarcts.

Not all investigators advocate prompt anticoagulation. In a retrospective study, Shields and associates found anticoagulant-related cerebral hemorrhage in five patients; four had been anticoagulated within 36 hours of the embolic event, two had been anticoagulated excessively and all had large initial cerebral infarcts.[14] They reviewed an additional nine similar cases culled from the literature and proposed a three- to four-day waiting period before anticoagulating patients with embolic infarction.

Summary of Risks and Benefits of Prompt Anticoagulation in Embolic Stroke

Recurrent cerebral embolism will occur within two weeks in 10% to 20% of patients with embolic stroke. The risk of reembolization appears to be similar in patients with rheumatic heart disease, myocardial infarction and nonrheumatic atrial fibrillation. Prompt anticoagulation with heparin may reduce the rate of early recurrent stroke from at least 13% to less than 5%. Hemorrhagic transformation of embolic infarcts occurs infrequently during heparin anticoagulation, develops spontaneously in some untreated patients and is not always clinically significant. The risks of systemic and central nervous system complications due to prompt heparin therapy appear to be outweighed by the possible benefits of therapy.

Management of Patients With Embolic Stroke

All patients admitted with cerebral infarction should have a CT brain scan to rule out hemorrhagic or mass lesions.[15] The possibility of embolic stroke should be considered if an appropriate underlying cardiac lesion is suggested from history, examination and electrocardiogram. If a lumbar puncture was part of the diagnostic evaluation, administration of heparin should be delayed two to four hours to avoid a small risk of spinal epidural hematoma[15]; otherwise, continuous intravenous heparin therapy should be started immediately. Long-term warfarin therapy will be required in patients whose underlying cardiac conditions pose a continued threat to recurrent embolization. The recommendation to anticoagulate promptly should be tempered in patients with very large infarcts, severe neurologic deficits, uncontrolled hypertension, CT evidence of hemorrhagic infarction or systemic lesions predisposing to hemorrhage. I would not recommend anticoagulating patients with the clinical appearance of embolic stroke in whom no underlying cardiac lesion can be found.

These recommendations are based on personal experience and assessment of the literature. As always, insufficient data foster controversy and differing opinions are abundant; nevertheless, early anticoagulation is being endorsed by an increasing number of neurologists.[3,4,7,8,10,12,16]

Stroke in Evolution

Stroke in evolution is a progressive clinical deterioration that shortly follows new symptoms of cerebral ischemia. The initial deficits may worsen or new deficits appropriate to the initially involved vascular distribution may appear. Progressive symptoms due to carotid thrombosis usually evolve within 24 hours—less than 4% of these patients will accumulate new deficits after 48 hours.[17] When basilar thrombosis underlies an evolving stroke, symptoms develop over a longer period of time—from 72 hours to as long as a week. Careful observation of patients with new cerebral infarcts should reflect these time courses.

The syndrome of stroke in evolution may, of course, be produced by lesions other than progressive vascular thrombosis. In one study, 42% of patients with stroke in evolution had nonischemic lesions, including hemorrhagic infarction, hemorrhage, tumor, subdural hematoma, aneurysm and arteriovenous malformation.[15] Lacunar infarction may also present in a stepwise, progressive fashion. These various causes must be excluded before starting anticoagulation; with the exception of subarachnoid hemorrhage, CT brain scan is more sensitive than lumbar puncture in their detection.[15]

The recommendation to anticoagulate patients who have evolving stroke derives from a small number of suboptimal studies. In some, stroke in evolution is not clearly defined or includes the progressive lethargy and worsening deficits that accompany postinfarction cerebral edema. Nevertheless, the data available suggest that anticoagulation may prevent progression of cerebral infarction; in the best designed study, progression was observed in 26/67 untreated and 9/61 treated patients.[18] These data are not so overwhelming that anticoagulation should be vigorously pursued in high-risk or questionable cases. For example, I would not anticoagulate a patient with progressive stroke if brain CT scan were not available. Lumbar puncture is too insensitive to exclude most hemorrhagic lesions, and, in this instance, the risks of anticoagulation might outweigh any possible benefits.

Anticoagulation in Cases of Transient Ischemic Attacks and Completed Stroke

In patients who have transient ischemic attacks, anticoagulation may possibly decrease the incidence of further attacks; however, anticoagulation does not appear to reduce the subsequent incidence of stroke.[19] Patients with vertebrobasilar TIAs may benefit from a brief course of anticoagulation, but after a year of therapy, the risks of hemorrhagic complications exceed the potential benefits.[20]

Before diagnostic angiography, anticoagulation is cur-

TABLE 2.—*Treatment of Cerebral Infarction*

Limit infarct size
Increase blood flow to ischemic zones
Decrease neuronal metabolism
Prevent new infarction
Anticoagulation
Antiplatelet agents
Surgery
Risk factor management
Prevent and treat complications
Phlebothrombosis in the hemiplegic leg
Pneumonia
Fluid and electrolyte disorders
Ischemic ulcers and contracture
Peripheral nerve pressure palsies
Late epilepsy
Depression

TABLE 3.—*Limiting Infarct Size*

Increase blood flow to ischemic zones
Vasodilators
Papaverine hydrochloride
Prostacyclin
Hypercapnia
Hypocapnia
Steal from normal to ischemic zones
Permit or induce hypertension
Streptokinase
Naloxone hydrochloride
Hyperbaric oxygen
Phlebotomy
Reduction of brain edema
Decrease neuronal metabolism
Barbiturate coma

rently used in the initial management of patients with frequent and recent TIAs. This practice is not based on clinical data, and aspirin may be a viable alternative when a preocclusive vascular lesion is not suggested clinically. There are theoretical reasons for preferring aspirin over heparin in these patients. First, heparin can increase platelet aggregation, an undesirable effect in patients with carotid artery TIA.[1] Second, some carotid artery TIA may be precipitated by plaque hemorrhage—a condition that heparin could conceivably aggravate.[21] Clinical studies are clearly needed to address these theoretical concerns.

Anticoagulation is of no proven benefit in patients with completed strokes of noncardiac cause.[11]

Management of Cases of Completed Stroke

There are three major goals in treating patients with completed stroke: limiting infarct size, preventing new infarction and preventing and treating complications. These are summarized in Table 2.

Limiting Infarct Size

A lesion resulting from cerebral infarction comprises two pools of neurons: dead cells, which are truly a lost cause, and ischemic cells, which may recover, remain ischemic and dysfunctional or go on to die. There are two general strategies for preserving and resuscitating this ischemic pool: to increase nutrient supply and to decrease metabolic demand (Table 3).[22]

Nutrient supply could be increased by augmenting blood flow to the ischemic region. This logical notion has two possible drawbacks. First, reperfusing a region of cerebral infarction can result in cerebral hemorrhage, as was discovered in the early attempts to revascularize occluded carotid arteries.[19] Second, ischemic zones may lose the brain's normal capacity for autoregulation of cerebral blood flow; hence, general cerebral vasodilators may steal blood from the passive ischemic regions while increasing perfusion of normal regions.[19,22,23]

The use of papaverine hydrochloride and hypercapnia as vasodilators has produced conflicting results in studies that are generally too small to allow definite conclusions.[19,22,23] Prostacyclin has been administered intravenously to small numbers of patients in open trials with encouraging results.[24] Inducing hypertension has transiently benefited a few patients, but is not generally recommended. Maintaining an adequate systemic blood pressure, however, would appear to be vital for the passive, pressure-dependent ischemic brain regions. In this regard, some degree of hypertension should be allowed in patients with chronic hypertension who would normally require a higher systemic blood pressure to maintain adequate cerebral perfusion.[25] Thrombolytic therapy using streptokinase and urokinase was not efficacious in several double-blind trials conducted in the 1960s.[11] Intracerebral hemorrhage developed in a number of treated patients, perhaps as a consequence of reperfusing ischemic or infarcted tissue. Administration of hyperbaric oxygen can increase function in ischemic regions but risks decreasing cerebral blood flow diffusely by reflex cerebral vasoconstriction.[19,22]

Considerable controversy surrounds the use of naloxone hydrochloride in patients with stroke. In a report from this institution, intravenous administration of naloxone transiently reversed the neurologic deficits of three patients with rather complicated neurosurgically related ischemic events.[26] In contrast, naloxone produced no improvement in a mixed group of 19 stroke patients at San Francisco General Hospital Medical Center.[27] It remains to be determined whether higher doses of this or other opiate antagonists will be beneficial for any subgroup of stroke patients.[28]

A hematocrit in excess of 45% is a risk factor for stroke.[3,29] Cerebral blood flow declines over a range of rising normal hematocrits and can increase in individual patients following phlebotomy. Phlebotomy may, therefore, be beneficial for those stroke patients with hematocrits in the mid to high 40s,[3,29] though this practice remains to be validated by controlled clinical trials.

Few measures are available to reduce neuronal metabolism. Hypothermia might be effective but has worsened ischemic infarction in animals, possibly by increasing blood viscosity.[22] Barbiturate coma can decrease neuronal metabolism and has been beneficial in several stroke models when induced before the ischemic lesion.[30] The results of small trials in cases of human ischemic infarction have been disappointing. Barbiturate coma prevents monitoring of the neurologic state and has adverse cardiovascular effects. Further studies will have to show benefits that outweigh these potential disadvantages.

Preventing New Strokes

Stroke is a significant risk factor for the development of further strokes.[2,3] One gram of aspirin per day significantly

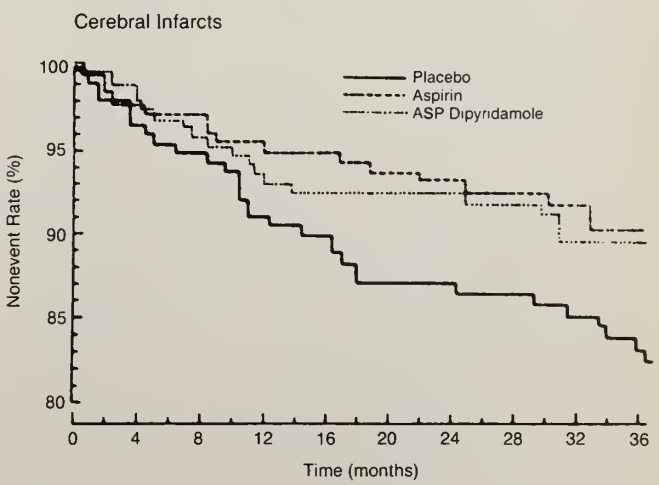

Figure 1.—AICLA (Accidents, Ischemiques Cerebraux Lies à l'Atherosclerose) study results: Distribution of fatal and nonfatal cerebral infarction (from Bousser et al[31]).

reduced the risk of subsequent stroke in both men and women with a recent stroke or TIA (Figure 1).[31] The benefits of lower aspirin dosages remain undetermined.[3] As mentioned earlier, anticoagulation can decrease recurrent embolic stroke. Risk factor management should never be overlooked in a stroke patient[3]; in particular, systolic hypertension should be treated, though, as already emphasized, this is most safely done after the acute phase of a stroke.

Preventing and Treating Complications

Cerebral edema arises within hours of cerebral infarction, peaks at between two and four days and resolves within two weeks.[22,32] An initial cytotoxic component occurs when ischemic and infarcted cells lose the capacity to maintain their functional and structural integrity. A vasogenic component arises subsequently. Cerebral edema can progress to brain herniation and death and, in milder forms, can extend the area of infarction by impairing cerebral microvascular flow.[19,22]

The treatment of ischemic cerebral edema is unsatisfactory. Steroids would not be expected to affect cytotoxic edema. Several prospective, double-blind studies have failed to show any benefit of steroids in stroke, and, in some instances, complications were higher in the steroid-treated patients.[32] Osmotic agents have also been disappointing. Mannitol is either ineffective or only briefly useful and may cause rebound intracranial hypertension following its withdrawal. Glycerol is metabolized by brain cells and may improve cerebral metabolism; however, clinical studies of its use in cases of ischemic cerebral edema have provided only equivocal evidence of benefit.[19,23,32]

Thrombophlebitis is an often-neglected stroke complication. Between 33% and 59% of stroke patients may have deep venous thrombosis that in most cases affects the hemiplegic leg.[19] Prophylactic minidose heparin therapy can reduce this high incidence fivefold without hemorrhagic complications[33,34]; clinical trials are warranted to see if aspirin can do as well.

Pneumonia is a common stroke complication that may be prevented by meticulous airway care and prophylactic intubation when a neurologic deficit compromises airway protection. For example, I would electively insert an endotracheal tube in a patient with a brain-stem stroke in whom cranial nerve dysfunction leads to pooling of secretions in the hypopharyngeal region.

Epilepsy arises in 6% to 15% of all stroke patients.[19,23] Seizures occurring within the first two weeks have a low likelihood of becoming recurrent; hence, long-term treatment with anticonvulsants is often unnecessary.[19,35] Seizures arising after the first two weeks, however, tend to be recurrent and should be treated over the long term with anticonvulsants.

Limb contractures and ischemic ulcers can be avoided by assiduous nursing care and physical therapy. Preventable peripheral nerve injuries occur when partially paralyzed limbs are left hanging or in contact with sharp or rigid objects—wheelchairs are notorious offenders here.

Finally, depression complicates the recovery from stroke in as many as 50% of patients. Although this depression is, in part, an appropriate response to a sudden loss of function, it is likely that cerebral ischemia also directly alters the level of important neurotransmitters. The early use of antidepressant medications may be beneficial for patients with severe depression.

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Epitomes
Important Advances in Clinical Medicine

Neurology

The Scientific Board of the California Medical Association presents the following inventory of items of progress in neurology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, research workers or scholars to stay abreast of these items of progress in neurology that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Neurology of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to Division of Scientific and Educational Activities, California Medical Association, 44 Gough Street, San Francisco, CA 94103

Intellectual and Behavioral Effects of Anticonvulsants

MOST OF THE major anticonvulsants, especially when used in combination, may interfere with intellectual function and behavior, at least in subtle ways. Attention, concentration, intellect, sociability, mood and motor activity may all be affected to some extent by these pharmacologic agents. For many patients with epilepsy the treatment becomes as much a problem as the disease.

Phenytoin

Familiar side effects from phenytoin include dysequilibrium and an acute encephalopathy. A more insidious impairment of mental function may occur without the usual clinical signs of phenytoin intoxication and in the face of therapeutic blood concentrations. This problem has occurred most frequently in children with brain damage and may be mistaken for progressive degenerative neurologic disease. Decline in IQ has been found. In adults progressive dementia may be mimicked, and an electroencephalogram may show excessive slowing. The syndrome is reversible with reduction of dosage or discontinuation of phenytoin therapy. Similar mental changes have been produced in subjects receiving phenytoin in the absence of epilepsy.

Barbiturates

Barbiturates have long been known to produce behavioral disturbances in children, especially hyperactivity, aggressive behavior, tantrums, sluggishness and disobedience. These complications may be seen in half of the children taking barbiturates and are troublesome enough to limit the usefulness of this medication, especially for relatively benign conditions such as febrile seizures. These behavioral disturbances are rapidly reversible with reduction of dosage or discontinuation of the use of barbiturates.

Benzodiazepines, Ethosuximide, Valproate, Carbamazepine

Benzodiazepines have side effects similar to those of barbiturates such as irritability, aggression and hyperactivity. Ethosuximide can produce psychosis or encephalopathy. Stupor and drowsiness occur occasionally with the use of valproate sodium. Significant behavioral disturbances are rare with the administration of carbamazepine and are found most frequently in patients with brain damage who are also receiving other anticonvulsants. Because intellectual and behavioral effects are unusual with the use of carbamazepine, that anticonvulsant may be the drug of first choice for tonic-clonic and partial complex seizures, at least in children.

Monotherapy

Many of these side effects are related to the use of several drugs in anticonvulsant therapy. By withdrawing multiple drugs and instituting a single drug, a clinician can frequently reduce or eliminate the intellectual and behavioral effects without significant harm to seizure control. Monotherapy is often the most effective method of seizure control, even for frequent seizures.

It must be stressed that intellectual and behavioral effects, sometimes subtle and sometimes resembling progressive neurologic deterioration, can occur at therapeutic anticonvulsant blood concentrations in persons with epilepsy. The benefits of therapy must outweigh the negative intellectual and behavioral effects. However, not all intellectual and behavioral abnormalities in epileptic children are related to medication; brain damage and social problems are often complicating factors irrespective of pharmacologic intervention.

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Alzheimer's Disease
(Senile Dementia of the Alzheimer Type)

In 1983 the number of persons in the United States older than 65 years surpassed the population of teenagers. By the year 2030, it is estimated that those older than 65 will make up about 20% of the total population—that is, *about 50 million persons.*

When elderly people begin to suffer memory lapses or periodic confusion, these symptoms are most often blamed on "old age" or senility, but may simply be "benign forgetfulness." The most serious common form of *acquired* mental deterioration is Alzheimer's disease, which probably affects more than 500,000 persons in the United States older than 40 years. The incidence increases with age (2% from 65 to 70 years; 4% from 70 to 80 years; 20% older than 80 years), but it is not synonymous with advancing age or senility. Siblings of patients have a 3.8% risk of having the disease; children of parents who have Alzheimer's disease have a 10% risk. Of interest is that there is an elevated frequency of Down's syndrome as well as leukemia and Hodgkin's disease among family members.

Senile dementia of the Alzheimer type was first described almost 80 years ago by a German neuropathologist and neurologist, Alois Alzheimer. The pathologic features are a loss of cortical and certain subcortical neurons, neurofibrillary tangles and senile plaques. It is a painless, progressive illness that commonly presents initially as a loss of memory and an inability to learn new material. Personality, behavioral and motor changes, such as rigidity or paralysis, and incontinence occur rather late in its evolution. Life expectancy is shortened. Death is commonly due to intercurrent infections, usually at a time when the patient is mute, withdrawn and requiring constant nursing care.

The cause of Alzheimer's disease is obscure. The most popular theories concern "slow viruses," "prions" (proteinaceous infectious particles) and disorders of the immune system, but *not* aluminum toxicity as once suggested. A decrease of choline acetyltransferase, somatostatin and norepinephrine content in the neocortex has been shown in some patients. There are no characteristic blood, urine or cerebrospinal fluid abnormalities. Electroencephalograms and computed tomographic scans show nonspecific abnormalities in the advanced stages. Positron-emission tomography and nuclear magnetic resonance are more likely to detect early abnormalities. Psychological testing shows changes consistent with "cortical" dementia. Because of the large number of conditions that can cause mental deterioration in adults, the diagnosis of Alzheimer's senile dementia is one best made by exclusion of other causes, of which about 10% are treatable. It is important to recognize and treat depressed patients who may present with dementia initially.

There are no specific treatments at present. Management involves guidance to family members and friends, treatment of intercurrent medical and behavioral problems and nursing home admission when a patient can no longer be cared for at home. Support groups exist in most large communities under the direction of: Alzheimer's Disease and Related Illnesses Foundation, 360 N Michigan Ave, Suite 601, Chicago, IL 60601.

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Anticoagulation Therapy for Cardiogenic Cerebral Emboli

The question of when to use anticoagulation therapy epitomizes the controversy surrounding the clinical management of stroke. Anticoagulation is often used routinely for stroke prophylaxis and urgent intervention even when solid evidence to support this therapy is lacking. There is, however, one clinical setting in which anticoagulation is definitely beneficial: preventing initial and recurrent cerebral emboli from a recognized cardiac source.

Chronic atrial fibrillation in the presence of rheumatic valvular disease is associated with a 17-fold increased risk of stroke in previously asymptomatic patients, and long-term anticoagulation appears to decrease this by 80% to 90%. Nonvalvular chronic atrial fibrillation carries a fivefold to sixfold increased stroke risk for asymptomatic patients; studies to establish a benefit from anticoagulation are currently in progress. Of patients with acute myocardial infarction, about 5% will suffer cerebral emboli in the first six weeks and remain at risk indefinitely even after that period; anticoagulation significantly decreases their risk of embolic stroke.

Patients having acute embolic stroke from a cardiac source are at high risk for recurrent emboli, particularly in the first week; this seems to be largely independent of the nature of their underlying cardiac disease. In general, immediate anticoagulation with heparin can be given safely and effectively in such cases, given that a noncontrasted computed tomographic (CT) scan of the head shows no evidence of hemorrhage. In a patient with clinical evidence of a large ischemic infarction, however, anticoagulation should be delayed until the CT scan is repeated in four to seven days; this is done specifically to rule out delayed spontaneous hemorrhage, an increasingly recognized complication of large embolic infarctions.

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Sensory Evoked Potentials

THE CLINICAL EVALUATION of patients with neurologic problems is subjective and based on semiquantitative data. Computed tomography (CT), other radiologic procedures, electroencephalography (EEG), electromyography and, in the future, nuclear magnetic resonance imaging contribute to the diagnostic acumen. An objective, noninvasive evaluation of specific spinal cord and brain sensory pathways has become available in clinical practice through the application of sensory evoked potential (EP) techniques. Sensory evoked potentials are the electrical responses of the nervous system to specific external stimuli that activate afferent pathways. These potentials are of very low amplitude, which requires that they be extracted from the much larger ongoing EEG activity using computer averaging techniques. Applications of clinical use are (1) cortical visual evoked potentials elicited by reversing pattern stimulation, (2) click-evoked brain-stem auditory evoked potentials and (3) electrically elicited subcortical and spinal somatosensory evoked potentials.

Visual Evoked Potentials

The primary usefulness of visual EPs is in cases of multiple sclerosis because the optic nerve is frequently involved in this disorder, even in asymptomatic patients, and abnormalities tend to persist after clinical recovery. The diagnosis of multiple sclerosis requires evidence of multifocality. Visual EPs often provide that information. In patients without clinical evidence of optic nerve involvement, visual EPs are abnormal in 40% to 50% of cases of possible and probable multiple sclerosis and in 50% to 60% of cases of definite multiple sclerosis. In other lesions of the optic nerve, visual EPs are not as useful because involvement is often clinically apparent or detected more easily by other techniques. Intraoperative monitoring of patients with tumors in or around the optic nerve is helpful in selected patients. Visual EPs are not helpful in the evaluation of coma.

Brain-stem Auditory Evoked Potentials

Brain-stem auditory EPs are not as useful in cases of multiple sclerosis, but the detection rate of silent lesions is still about 20% to 30%. This technique is excellent in the early detection of acoustic neuromas and invasive brain-stem gliomas. The yield in detecting acoustic neuromas, even very small ones not visualized by contrast brain CT scan, is well over 90%. Normal findings on brain-stem auditory EPs, for all practical purposes, rule out an acoustic neuroma. In some selected patients brain-stem auditory EPs are used to monitor the functional integrity of the acoustic nerve during removal of an acoustic neuroma. This technique has not been useful in detecting vascular lesions of the brain stem. In patients in coma, normal brain-stem auditory EPs are highly suggestive that the brain stem is functionally intact. Abnormal evoked potentials in a patient in coma imply that the primary cause of the coma is a structural brain-stem lesion.

Somatosensory Evoked Potentials

Somatosensory EPs are also excellent in detecting silent lesions in cases of multiple sclerosis. In patients without sensory symptoms or signs, somatosensory EPs will be abnormal in 50% with a definite diagnosis of multiple sclerosis, in 55% to 60% with a probable diagnosis and in 40% with a possible diagnosis. These percentages will be even higher when both upper and lower extremity stimulation is used. In addition to cases of multiple sclerosis, somatosensory EPs are sometimes of use to locate lesions in the peripheral nervous system, plexi, roots and spinal cord. Abnormalities will be present when posterior columns or the lemniscal system is involved. Because somatosensory EPs test different structures than brain-stem auditory EPs, they are helpful in evaluating cases of coma. Normal somatosensory EPs and brain-stem auditory EPs in a patient in coma make it extremely unlikely that the cause of the coma is a structural brain-stem lesion. Monitoring spinal cord function with somatosensory EPs in patients undergoing an extensive spinal operation is only feasible in centers with special expertise in this area.

Sensory EP studies can be of help in the diagnosis of neurologic disorders when used in situations as described above. Their indiscriminate use because they are available, relatively cheap and noninvasive should be discouraged.

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Arteriographic, Digital Angiographic and Noninvasive Testing of the Carotid Arteries

JUST TWO YEARS ago intravenous (IV) digital subtraction angiography was touted as a minimally traumatic method that would replace both standard head and neck arteriography and noninvasive tests in assessing disease in the carotid systems. Today it is clear that each neurodiagnostic technique has its place. Standard arteriography provides high-resolution images of the extracranial and intracranial vessels that cannot be achieved yet with IV or intraarterial digital subtraction angiography. The latter offer maximal contrast resolution, whereas the standard arteriographic techniques offer maximal spatial resolution. The noninvasive tests, using primarily ultrasound and plethysmographic methods, are the most sensitive procedures for detecting physiologic changes in the carotid and ophthalmic systems, which one can use to determine the hemodynamic effects of a carotid stenosis and to interpolate residual lumen diameter. Using noninvasive tests to monitor physiology is the safest and most practical way to follow patients for evidence of progression of a carotid lesion.

Although IV digital subtraction angiography is a relatively atraumatic technique and can be done on an outpatient basis, it carries associated local, systemic, cardiac and neurologic risks. Even when done well, the findings may be obscured by overlapping of vessels, poor cardiac output and subtraction and movement artifacts. The frequency of inadequate studies may increase with the occurrence of bilateral and tandem atheromatous lesions. Noninvasive tests are less traumatic and more routinely applicable, but not easy to carry out well. Neither noninvasive tests nor IV digital subtraction angiography provide data by which one can consistently distinguish between an occlusion and very tight stenosis or reliably identify ulcerations in an atheromatous plaque.

Patients with an asymptomatic bruit should be examined first with noninvasive testing. Patients with ischemic events

in one vascular territory in whom noninvasive testing shows no evidence of contralateral or tandem lesions are candidates for IV digital subtraction angiography. If a patient has several signs or symptoms in several vascular territories or evidence of multiple lesions on noninvasive testing, an intraarterial contrast study is recommended. This should be a standard arteriogram unless selective catheterization is difficult. In the latter case, intraarterial digital subtraction angiography can facilitate the relatively rapid acquisition of information on the extracranial or intracranial extracerebral vessels using modest contrast volumes.

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Magnetic Resonance Imaging Versus Computed Tomography

X-RAY COMPUTED TOMOGRAPHY (CT) has revolutionized diagnosis and management. The information gained from CT scans has contributed to a reduction in the number of electroencephalograms, angiograms, spinal taps, plain skull films and isotope scans formerly done largely as nonspecific screening procedures. With the additional tomographic data available from magnetic resonance (MR) imaging, there will likely be a further reduction in these procedures.

A CT scan shows bone, blood and some grey and white matter distinction, but because the possible interactions of x-rays and tissues are limited, very little soft tissue characterization is possible. Magnetic resonance allows the imaging of hydrogen in tissues by applying a complex sequence of fixed and changing magnetic fields to a region of the body. A patient is placed in a very strong, constant magnetic field, several thousand times the earth's magnetic field. While this field is held constant, a high-frequency alternating current (in the shortwave radio range) is superimposed on this main field for a brief period. This excites hydrogen nuclei in the tissues. About two thirds of a body's atoms are hydrogen. The nucleus of the hydrogen atom behaves like a small bar magnet and tends to orient parallel to the main field. When excited by the radiofrequency pulse, some nuclei are driven out of alignment, returning to their original alignment after about one second. During this return, or decay, time they emit a radio signal at a frequency proportional to the magnetic field they are in. By adding and subtracting from the main field by electromagnetic coils placed around the patient, slight gradual changes (gradients) in field strength between two positions within the patient can be made that cause the resonant frequency of the decaying signal to be position-dependent. By this means, location and imaging of hydrogen in the body are possible.

Magnetic resonance excitation is usually by means of a sequenced pair of pulses separated by a brief interval. The computer expects tissue to be in the same place for both. If blood is moving rapidly, it will not be in the same place and will have been replaced by unexcited hydrogens. The chambers of the heart and the lumina of large vessels therefore appear dark. Blood's movement serves as its own contrast medium. It is reasonable to expect that most angiography (including coronary) eventually will be done by this noninvasive method. Within the limitations of patient movement, spatial resolution is as good as the best CT scan. Other characteristics of hydrogen's resonant frequency and rates of decay of the hydrogen signal provide still more information about tissue characterization.

Cortical bone contains very little hydrogen, so it appears black and is invisible on a scan. Many ordinarily obscured soft tissues such as bone marrow, pituitary, posterior fossa, spinal canal and inner ear structures can be seen with unprecedented clarity. Malignant tumors, edema and inflammation can be differentiated clearly from surrounding healthy tissues because tissue water in these regions is not only greater but appears to be relatively unbound to large molecules and cellular structures.

Magnetic resonance imaging produces so much information without the need to inject contrast material that there is little stimulus to develop new contrast media. And because there is no ionizing radiation, magnetic resonance appears to be completely harmless.

At present the greatest limitations of MR imaging are its long scan time (more than five minutes, making it inappropriate for many patients); its high cost (almost twice as much as a CT scanner); its low patient load (about half of that of CT); its complexity of theory, operation and interpretation (an order of magnitude greater than CT); its large space requirement (several times that of CT), and government resistance to this new technology.

The technology of CT was an order-of-magnitude jump over simple shadow radiography. Magnetic resonance appears to involve a similar jump beyond CT because it offers so much more information about tissues without subjecting patients to ionizing radiation. It should not be considered simply an extension of x-ray CT.

Because it is not radiologic in nature and is so complex, MR imaging will offer so much information to so many specialties that the performance and interpretation of this remarkably diverse new clinical probe of tissues inevitably will become interdisciplinary and not confined to any one specialty.

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Percutaneous Glycerol Trigeminal Gangliolysis for Tic Douloureux

TIC DOULOUREUX is a well-known syndrome of facial pain usually characterized by unilateral, paroxysmal, lancinating, electric shock-like pains in the distribution of one or more branches of the trigeminal nerve. The pain is unique in that it is frequently evoked by nonnoxious ipsilateral (trigger zone) stimulation, and neurologic examination shows little detectable trigeminal sensorimotor deficit. Episodes of pain last

only seconds but recur with a variable frequency, usually in clusters and lasting from days to months. There are often spontaneous remissions for weeks, months or years between flurries of attacks.

About 70% of patients will obtain relief with the use of either carbamazepine or phenytoin. Thus, in about 30% of patients, medication is either ineffective or produces serious side effects necessitating discontinuance. These patients, therefore, may be candidates for the various surgical procedures that have been designed to treat tic douloureux. The mainstays of surgical therapy for this disorder are microvascular decompression of the trigeminal nerve via posterior fossa craniectomy, or percutaneous radiofrequency trigeminal gangliolysis. The former procedure has the potential of producing long-lasting pain relief without facial sensory loss, while the latter procedure avoids the risks of craniectomy and can be repeated easily if tic pain recurs.

Recently, retrogasserian injection of glycerol through a spinal needle inserted percutaneously into the trigeminal cistern has been shown to be an additional effective method of treating tic douloureux. The procedure is done with the patient awake under local anesthesia, and it is generally well tolerated. Pain relief from this procedure does not depend on producing sensory loss and there seems to be less likelihood of troublesome facial dysesthesias. Rare complications include corneal anesthesia and keratitis. More than two thirds of patients can expect pain relief for six years or longer and the procedure can be easily repeated in the event of pain recurrence. Experimental studies seem to indicate that the therapeutic effectiveness of glycerol in the treatment of tic douloureux is based on its nonspecific neurolytic effect, which may interfere with abnormal impulse generation within the nerve. Glycerol gangliolysis may represent a major advance in the treatment of tic douloureux because it is easily done, well tolerated by patients and produces much less facial numbness than other available neurodestructive procedures.

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Migrainous Stroke—New Therapeutic Considerations

MIGRAINE IS A common disorder, present in about 5% to 10% of the general population. The clinical spectrum of migraine varies widely, from patients with infrequent mild head pains to the unfortunate group with incapacitating pain. When the neurologic features of a migrainous episode, classically thought to result from vasospasm, dominate the clinical presentation, the term "complicated migraine" is used. In some patients with complicated migraine, the vasospasm is apparently so severe or prolonged, or both, that brain tissue in the distribution of the involved vessel suffers irreversible ischemic damage, evident clinically as stroke. Aggressive migraine prophylaxis is obviously indicated in this relatively small population of patients.

Several recent clinical studies have indicated that treatment with a calcium channel blocker (specifically, verapamil) may be useful in migraine prophylaxis for patients in whom more conventional agents fail. This class of agents may prevent migraine and, in particular, its vasospastic complications, both by inhibiting vascular smooth muscle contraction and by direct antiplatelet effects. Such actions would be especially desirable for patients at risk for migrainous stroke. Propranolol hydrocholoride, however, a drug widely used for migraine prophylaxis, may actually precipitate or prolong vasospasm through potentiation of α-adrenergic agonist vasoconstriction.

In patients considered at risk for migrainous stroke—specifically, those in whom the neurologic accompaniment is pronounced or persistent—ergot therapy is to be avoided. Propranolol may also prove unsuitable. Verapamil, in a dose of 80 mg three or four times a day, should be strongly considered for these patients. Other calcium channel blockers such as nifedipine may possibly be more effective, but verification is lacking at this time.

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When to Stop Anticonvulsant Therapy

BECAUSE OF potential side effects from long-term therapy, anticonvulsant therapy should be discontinued in patients with epilepsy as soon as there is a reasonable certainty that seizures will not recur. In practice, defining the point at which this reasonable certainty exists is a difficult question. More information is available for children than for adults. Studies of large numbers of children, with long follow-up, consistently show that about a quarter of patients who are seizure-free for four years while receiving anticonvulsant medication will relapse when the medication is withdrawn. Adults probably have a greater chance of relapse, though the precise relapse rate is not known.

There are clinical and electroencephalographic features that can identify patients who have a greater than average probability of relapse. Patients whose epilepsy took more than five years to control and those with intellectual impairment or other static neurologic abnormalities have relapses more than half the time. The presence of focal or mixed seizure disorders or the occurrence of unequivocally epileptiform abnormalities on an electroencephalogram predict a high relapse rate.

Certain forms of epilepsy have consistent clinical and electrographic features that serve to characterize them as benign epileptic "syndromes," including typical absence seizures with 3 cps spike-and-wave complexes that occur in children of normal intelligence. Similarly, children with focal motor epilepsy who have midtemporal and central spikes (the so-called benign focal epilepsy of childhood or Rolandic epi-

lepsy) should be considered to have a much lower than average relapse rate. Patients with these epileptic syndromes whose seizures have been controlled for four years should be considered for withdrawal of anticonvulsant therapy.

Certain potentially reversible illnesses may include recurrent seizures as part of their course. For example, metabolic derangements such as nonketotic hyperglycemia and profound hyponatremia may lead to frequent seizures that are difficult to control. Patients with alcoholism may have withdrawal seizures. None of these patients would be considered to have epilepsy, and anticonvulsant medication should be withdrawn when the underlying illness has resolved.

It appears reasonable to attempt withdrawing anticonvulsant therapy from patients, particularly children, whose epilepsy was easily controlled, who have been seizure-free for four years, who have at least average intelligence and normal neurologic function and whose electroencephalogram shows no abnormalities. This approach can be expected to yield the lowest incidence of relapse following withdrawal of medication.

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Neurologic Manifestations of AIDS

THE ACQUIRED immunodeficiency syndrome (AIDS) may be complicated by neurologic dysfunction in 30% to 40% of cases. Neuropathologic abnormalities, however, are found in about 70%; this may reflect the fact that subtle neurologic signs and symptoms may be overlooked in patients with severe systemic illnesses. In about 10% of patients with AIDS, the neurologic syndrome is the initial clinical manifestation. In such cases, herpes zoster radiculitis and aseptic meningitis are the most common harbingers.

Paralleling the nonneurologic effects of AIDS, the neurologic manifestations are most often due to opportunistic infections or malignancy. Meningoencephalitis, which may be acute or chronic, is the most common neurologic syndrome. In nearly 100 reported cases, most with brain abscess formation, *Toxoplasma gondii* has been implicated. About 60 cases of probable viral encephalitis have been reported, and although the specific virus has not always been discerned, both cytomegalovirus and herpes simplex virus have been cultured from the brains of such patients. *Cryptococcus neoformans* meningoencephalitis is third in frequency, with 33 cases reported. Less frequently implicated are other fungi, mycobacteria and spirochetes. Progressive multifocal leukoencephalopathy has also been reported.

Neoplastic involvement of the nervous system has been reported in 26 instances, including cases of primary brain lymphoma, metastatic lymphoma, meningeal lymphomatosis, epidural spinal cord compression and metastatic Kaposi's sarcoma.

Cerebrovascular complications, associated with nonbacterial thrombotic endocarditis, neoplasm and thrombocytopenia, have been reported in nine cases.

Peripheral nervous system complications occur less often (51 cases). These include chronic inflammatory polyneuropathy, distal symmetric neuropathy, cranial neuropathies due to lymphoma or inflammation, herpes zoster radiculitis and polymyositis.

Algorithms have been published for evaluating AIDS cases in which there are nervous system complications. Several caveats are noteworthy: first, toxoplasmosis is not ruled out by a negative computed tomographic scan or by "nondiagnostic" titers. Second, a cryptococcal antigen test may be positive in acellular spinal fluid. Third, herpes simplex encephalitis may be atypical in course and anatomic distribution in patients with AIDS. Last, different brain abscesses in the same patient may be due to different organisms.

Treatment is outlined by Snider and co-workers and Levy and colleagues. Frequent infectious recurrences, especially with *Toxoplasma* and *Cryptococcus*, raise questions about the duration of therapy.

Unfortunately, the overall prognosis is very poor in a patient with AIDS, with or without nervous system dysfunction. However, the nervous system complications themselves are frequently rapidly fatal if not diagnosed and treated; thus, such treatment may improve both quality and quantity of life in a patient who has AIDS.

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Medical Ethical Issues

MODERN RESUSCITATIVE TECHNIQUES, including ventilator support, often produce ethical dilemmas in treatment decisions for patients with two types of severe brain damage: brain death, in which the patient shows a complete loss of all brain functions, both cerebral hemisphere and brain stem; and states of permanent unconsciousness. One example of the latter is a persistent vegetative state in which deep coma evolves over a few days or several weeks into a condition of eyes-open unresponsiveness and sleep-wake cycles. Physicians and patients' families are increasingly questioning the indeterminate use of life-sustaining techniques for patients who are brain dead or who are extremely unlikely to return to cognitive, sapient life. The first group of patients is, by definition, medically and (but for a pronouncement) legally dead in most American states; the second group is very much alive and must be recognized as such.

The 1981 *President's Commission Criteria*, now the nationally accepted and most current standard for the clinical determination of brain death, superseded the 1968 *Harvard Criteria*. Neurologists (or, when appropriate, neurosur-

geons) should be consulted to confirm the diagnosis because conditions that mimic brain death but are often reversible—such as drug and metabolic intoxication, hypothermia and shock—may exist. Once physicians have made a careful determination of brain death, they should discuss the concept with the patient's family and explore the possibility of organ donation, if clinically feasible and otherwise appropriate. After a patient has been pronounced dead, removing the ventilator has no greater ethical or legal significance than stopping any other treatment for a dead patient.

Permanently unconscious patients present a different problem. Legal concerns added to the inherent limitations of neurologic prognoses frequently make physicians hesitate to classify patients as permanently unconscious. After a sufficient period of observation and adequate clinical evaluation, a physician's confidence in the diagnosis of permanent unconsciousness may lead to a favorable response when the patient's family or surrogate (a legally recognized representative of the patient) requests the withdrawal of treatment, thus allowing the patient to die.

These requests create an ethical issue. In 1981, both the Judicial Council of the American Medical Association and the Los Angeles County Medical Association—supported by the Council of the California Medical Association—endorsed the ethical propriety of withdrawing ventilator support from patients in an "irreversible coma" (a state of permanent unconsciousness), so long as the family concurred and the patient had expressed no contrary wish before the neurologic crisis. In 1983, a Presidential Commission urged that patients' families be recognized as primary decision makers in such cases, stating that "the law does not and should not require any particular therapies to be applied or continued, with the exception of basic nursing care that is needed to ensure dignified and respectful treatment of the patient." In addition, a California appellate court dismissed criminal charges against two physicians in a 1983 case involving the discontinuance of both ventilator and fluid support for a deeply comatose patient. The court held that a physician has no duty to continue treatment that will not improve a patient's prognosis for recovery, that has become futile and that offers no reasonable medical benefit to the patient in terms of a return to a "normal, functioning, integrated existence."

Antibiotics, blood products, cardiac drugs, dialysis, pressor agents and ventilators all might be used as life-sustaining treatment for permanently unconscious patients. No logical distinction can be made among these modalities for such patients. When the family or surrogate concurs and when the decision does not conflict with the values of the patient, physicians may ethically withhold or withdraw all such forms of life-sustaining treatment. There is a caution, however. The provision of fluids and nutrition holds a deep emotional and symbolic significance for many professionals and lay persons, who see it as one element of "basic care" for such patients. To withdraw food and fluids may generate extreme controversy and even lead to sanctions.

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Interventional Neuroradiology

INTERVENTIONAL NEURORADIOLOGY has recently become an accepted treatment method for selected cases of brain and head vascular abnormalities. Treatment is carried out endovascularly, generally through an angiography catheter, and may be divided into two basic types: the opening of arteries that are too narrow and the closing of blood vessels that supply hypervascular abnormalities (arteriovenous malformations, arteriovenous fistulae and vascular neoplasms).

Unlike other areas of the body, the end organ (the brain), is unforgiving of careless technique. Introducing either atheromatous or inappropriately placed iatrogenic emboli into its circulation has grave consequences.

Starving hypervascular lesions of the brain and scalp is done by introducing small foreign particles—usually polyvinyl alcohol foam sponge particles, Gelfoam particles or silicone spheres—selectively into the arteries supplying the lesion through percutaneously placed angiography catheters. For arteriovenous malformations of the brain, one depends on the high flow into the lesion to carry the emboli to the correct place. Introducing tissue adhesives via selective intracranial catheterization may also be undertaken, but it is still considered an experimental procedure and is reserved for life-threatening situations. The goal is to control headache, reduce steal symptoms and lessen the likelihood of second or subsequent hemorrhage (this latter point has not been definitely proved and is controversial). Treating scalp arteriovenous malformations is significantly less difficult and is also safer than treating intracranial arteriovenous malformations. One may catheterize the external branches of the carotid artery and, by using direct fluoroscopic real-time visualization of the embolic process, may completely occlude the blood supply to these lesions. A knowledge of the anatomy of the blood supply of the cranial nerves is essential for maximal patient safety. Though meningiomas may be controlled surgically, there appears to be some advantage in preoperative embolization five to seven days before an operation to allow peritumoral edema to regress before the operative intervention.

It is particularly satisfying for a therapist to encounter a traumatic carotid artery to cavernous sinus fistula, as embolic results are excellent. The therapist may guide a small detachable balloon-tipped catheter into the cavernous sinus and then, using real-time fluoroscopic control, gradually inflate the balloon until flow through the fistula has been stopped. The goal of the treatment is to preserve the internal carotid artery. Acceptance of this procedure is now widespread, and few operative approaches are thus done for traumatic arteriovenous fistulae. One expects the development of third, fourth and sixth nerve pareses in from 20% to 30% of patients; the paresis resolves over the course of three to six months.

Grüntzig balloon dilatation of atheromatous vessels has been recently reported as treatment for narrowing of the prox-

imal brachiocephalic and vertebral arteries. Relatively few reports detail dilatation of the more common narrowing of the internal carotid artery bifurcation. Physicians doing this procedure note the importance of identifying and excluding from treatment patients who have ulcerated plaques. Special precautions are taken to decrease the likelihood of downstream embolization. Follow-up for this procedure is short but the early results are promising.

Patients are prepared for embolic procedures with steroids; the steroid dosages are tapered over the three days following the procedure. The advantage of embolic techniques is a considerable reduction in costs. Patients leave the hospital on the second or third posttreatment day. Complications of embolic and dilatation procedures appear to be similar in quality and rate to the surgical approach for these diseases.

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Editorials

Magnetic Resonance in Medicine

ABBREVIATIONS USED IN TEXT

ATP = adenosine triphosphate
CT = computed tomography
MR = magnetic resonance

ALTHOUGH nuclear magnetic resonance (MR) was first described in the late 1940s almost simultaneously, but independently, by Bloch[1] of Stanford University and Purcell[2] of Harvard University, the technique was applied only in analytic chemistry for two and a half decades. Following the discovery of computed x-ray tomography, Lauterbur[3] of New York in 1973 published a paper indicating the possibility of generating three-dimensional images by a method that allowed the localization of radiofrequency signals within a volume. Very rapidly thereafter, important developments took place [4,5] and within a span of years we were able to see images with surprising degrees of spatial and contrast resolution. This newly emerging imaging technology was applied first to the central nervous system, which was not unique to magnetic resonance for the same was true of other important developments in imaging technology. For instance, cerebral angiography developed before angiography of other organs; ultrasound was first described in its applications to the brain; radionuclide brain scanning was also described early for the detection of brain tumors, and, of course, x-ray computed tomography was first applied to the brain. This is partly because it is difficult to examine the brain by external means and because the brain does not move and is very frequently involved in pathologic processes of all types. Thus, the article by Kucharczyk and coauthors appearing in this issue is very much in keeping with this tradition. To be sure, magnetic resonance is being applied to other organs in the body: the abdominal organs, the chest—including the mediastinum and particularly the heart—and also to the soft tissues and bones of the extremities. However, there are a number of technical difficulties in imaging the abdominal organs and the thoracic cavity due chiefly to the presence of respiratory and pulsatile motion, which tends to degrade the images. Much work is going into solving this problem, and techniques are being worked out to obtain images with gating of the heart via electrocardiographic control and gating for respiration. The latter is somewhat more difficult but I have confidence in their ultimate solution.

If we apply our relatively recent experience with x-ray computed tomography (CT), we can predict that there will be a slower development and a relatively slow learning curve for all of us in all areas outside of the central nervous system. CT made its appearance in the United States in the summer of 1973 and by the end of 1974 it was well established as a method of examining the brain. However, three years later, in 1977, we still did not have approval for payment of body CT examinations by the Health Care Financing Administration and most third-party payers, as its usefulness in body imaging was still in question.

Although MR clinical images of the brain were only obtained a little more than four years ago, we already count on systems capable of excellent spatial and density resolution.[6] It has also been shown that in the central nervous system, magnetic resonance imaging is already superior to CT in a significant number of areas. It is probably the method of choice to examine infants and children because of the absence of ionizing radiation and because of the ability of magnetic resonance to depict soft tissue detail much better than CT. For instance, the degree and the progress of the myelinization process in infants can easily be shown by MR but cannot be evaluated by CT. Thus, I believe that MR is ready for clinical application and that individual patients and third-party payers should accept this new modality in the special areas where it has been shown to be superior to CT. This list includes most areas with the possible exception, at the moment, of acute trauma, uncooperative patients, patients who carry cardiac pacemakers and seriously ill patients who may need life-support measures. In this last category, however, the problem can be solved by keeping the metal objects outside the room and bringing only hoses and wires into the magnet room.

One of the more attractive features of magnetic resonance is the potential for obtaining images of other elements such as sodium, phosphorus and fluorine. Indeed, images of sodium have already been obtained and the increase in the sodium content in a recently ischemic area of the human brain has already been shown.[7,8] It is also possible to obtain in vivo spectroscopy, which has been termed topical magnetic resonance. These in vivo phosphorus spectra can show rapid changes in the energy metabolism of the tissues by demonstrating adenosine triphosphate (ATP), creatine phosphate, inorganic phosphate and sugar phosphate. In animals it can be shown that rapid changes do take place in inorganic phosphate, creatine phosphate and ATP in brain ischemia and it can be expected that this procedure will be applicable to the human brain within a short period of time. Considerable interest has been aroused by the possibility of doing proton chemical shift imaging. The term is applied to the observation that protons produce different spectra depending on the place in a molecule where they are located.

It is already apparent that magnetic resonance is the procedure of choice to examine a patient who may have brain or spinal cord disease of a subacute or chronic nature and, with some exceptions, in acute conditions in cooperative patients. This includes infants and children who may require some sedation. In a consecutive series of cases of brain tumor examined at the Massachusetts General Hospital, magnetic resonance was capable of detecting the presence of intracerebral tumors in 100% of symptomatic patients, whereas computed tomography detected only 94% of lesions in the same group.

In general, physicians try to offer their patients the best in their judgment without regard to costs and they prefer the safest possible method to arrive at a diagnosis. Concerns for the rising costs of medical care may well delay the introduc-

tion of MR into daily practice, but it is hoped that the American traditions for allowing patients to receive the best that science has made available will prevail. Obviously, if physicians conclude, after careful study and evaluation, that MR is the method of choice to detect and characterize certain diseases, it should be used in preference to other approaches. This perhaps should be considered a patient's right.

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The Need to Support Organized Medicine

As we enter the second half of this decade one senses an impending economic crunch for physicians and patient care. Forces, seemingly beyond any control, are rampant in health care and significant economic pressures are already affecting both physicians and patients. Issues of economic survival in practice seem likely to affect many physicians and issues of rationing of care seem likely to affect many patients. Already some practicing physicians have noted reduction in their incomes, and this in the face of rising costs over which they have little or no control. Some patients are beginning to experience de facto rationing of care in some of the health care programs in the West, and elsewhere. And, to be candid, we probably "ain't seen nothin' yet." Realistically, it is likely that things will get worse before they get better, since the supply of dollars available for patients is not and never will be adequate to meet all of an ever-increasing demand.

What to do? Frustrated and feeling powerless, and sensitive to a personal economic pinch, some physicians understandably feel that somehow their leaders and their dues-supported organizations should not have allowed all this to happen; and since it is now happening, they should be doing something more about it. A present danger is that physicians who are frustrated, resentful and perhaps under some economic stress, will tend to withdraw their support of organized medicine just at the time when they need it most and it needs them most. If individual physicians or organized medicine are "to do something about it," all should rally around and individually and collectively identify what needs to be done and then do it. What is needed is more support by physicians for organized medicine and for each other—not less. A scattering or fragmentation of physicians at this time cannot be in either their individual or professional interest. Nor will it be in the interests of patients who will need the individual and collective advocacy of their physicians and organized medicine as never before.

The reality is that medical associations and organized medicine were never in a position to prevent either the rising costs of health care nor the rising concern among the public and private payors of these costs. Nevertheless, individual physicians and the organized profession can now "do something about it" in many ways. They can help to eliminate unnecessary costs and improve efficiency in health care delivery. This they can do, should do and are doing; already there is much being accomplished. But in the final analysis, when one gets to the bottom line of a limited number of health-care dollars and an ever-increasing public need and demand for health care services, one can see that there will be inescapable pressures to reduce the number and quality of health-care services that are rendered. It is here at this bottom line of health care that individual practicing physicians and physicians collectively in their professional organizations must stand and be counted. And it is here that individual physicians and their professional organizations will need the active support of all physicians in their own and their patients' interests.

To paraphrase an old expression, "Now is the time for all good physicians to come to the aid of their medical associations" in order to protect, preserve and promote adequate patient care of good quality. Membership retention and membership recruitment are now more urgent than ever before. This is essential, and clearly in the economic interest of all concerned.

MSMW

Polyamines in Biology and Medicine

Virtually all eukaryotic cells contain significant amounts of the polyamines spermidine and spermine and their precursor, putrescine. Although the specific physiologic functions of these polyamines are still not well understood or well defined at a molecular level, extensive recent studies have shown that their concentration is highly regulated and that cellular proliferation and differentiation require polyamine biosynthesis.[1-3] The availability of new reagents for specifically modulating the polyamine pathway has led to a tremendous resurgence in investigations of the fundamental role of these polycations and of the therapeutic efficacy for selectively blocking the synthesis pathway.[2-4]

The interdepartmental conference at the UCLA School of Medicine on "Polyamines in Clinical Disorders" presented in this issue is very timely and provides a brief overview of the polyamines, their synthetic pathway and the potential significance of polyamines in the physiologic function of many body organ systems. The conference participants discuss the potential clinical applications of inhibitors of polyamine biosynthesis in neoplastic disorders, pulmonary oxygen toxicity and skin disorders including psoriasis. The authors underline the fundamental importance of polyamine metabolism in cell function and describe the biologic clues suggesting the relationship of normal and altered polyamine metabolism to clinical disorders.

The role of polyamine biosynthesis in the proliferation of tumor cells is receiving renewed attention, and manipulation of this pathway for therapeutic purposes is a much-sought-after goal.[2-4] Dr Marton provides extensive evidence that the inhibition of polyamine synthesis influences the cytotoxicity

of antineoplastic chemotherapeutic agents.[5-7] His data show that inhibitors of polyamine biosynthesis can modulate reactions between DNA and drugs that alkylate DNA, altering the cytotoxicity of the agents studied in a time-dependent and agent-dependent manner. He also appropriately stresses that careful consideration must be given to the fact that inhibitors of polyamine biosynthesis also affect rapidly growing normal tissues such as the gastrointestinal epithelium[8] and hematopoietic cells.[9] For this reason, inhibitors of polyamine biosynthesis used in combination chemotherapy protocols must be given in the correct sequence and at the correct doses to maximize tumor cell kill and to minimize toxicity to normal tissues.

In addition to the potential importance for neoplastic diseases, inhibitors of polyamine biosynthesis may prove important in the treatment of other disorders. Dr Hacker presents tantalizing data which show that oxygen-induced pulmonary toxicity and its subsequent repair are importantly modulated by polyamines. He and other investigators have also shown that the development of medial hyperproliferation in the pulmonary vasculature, which leads subsequently to pulmonary hypertension, is dependent upon increased polyamine biosynthesis and may be attenuated by the use of inhibitors of polyamine biosynthesis.[10]

Dr Lowe discusses the induction of ornithine decarboxylase by ultraviolet irradiation, and points out that this induction of epidermal ornithine decarboxylase is inhibited by triamcinolone and indomethacin.[11] It appears that hyperproliferation in the epidermis may be polyamine dependent. In psoriasis, involved skin is characterized by hyperproliferation, accompanied by increased ornithine decarboxylase activity and increased polyamine content. Although preliminary findings suggest that topical administration of the inhibitor of polyamine biosynthesis, difluoromethylornithine, did not have a significant effect on epidermal proliferation or clinical signs in psoriasis,[12] the use of other modulators of polyamine biosynthesis, such as retinoids, may ultimately prove useful in the treatment of psoriasis.

A role for polyamines in the proliferation of cells and tissues has been clearly documented, and the clinical disorders described by the discussants are characterized by hyperproliferation in which increased polyamine metabolism has been implicated. Nevertheless, there is currently evidence for a clear long-term therapeutic benefit of the polyamine biosynthesis inhibitor, difluoromethylornithine, only in parasitic disorders, including trypanosomiasis.[4,13] In order for modulation of polyamine biosynthesis to become an achievable therapeutic modality, more research in several areas may be required. First, we need more compounds that will specifically inhibit steps in polyamine synthesis. For example, the currently available specific inhibitor of ornithine decarboxylase, difluoromethylornithine, is not uniformly effective in all organs and tissues.[14] In particular, it does not induce any significant suppression of cellular spermine levels. The development of inhibitors with higher potency that inhibit subsequent steps in the synthetic pathway might help achieve an increased in vivo antiproliferative effect.[4]

Second, despite the extensive literature on polyamine metabolism and its relationship to cell proliferation, the exact physiologic functions of the polyamines are still unknown. Basic aspects of polyamine metabolism such as the importance of turnover of polyamine pools, the precise sites of polyamine interconversion, the characterization of enzymes in the biosynthetic pathway other than ornithine decarboxylase and transport of polyamines into cells and tissues remain to be elucidated further.[1-3] In this regard, the recent availability of bacterial and mammalian cell mutants with defects in the biosynthetic pathways will permit studies delineating the relative importance of the various biosynthetic steps and enzymes in polyamine function.[1,15,16]

Molecular biologic techniques will also help in our understanding of the relationship of polyamine metabolism to cell proliferation. The mammalian gene that encodes for ornithine decarboxylase has been cloned by several laboratories using cells that were induced to overproduce ornithine decarboxylase.[17-19] Using the specific ornithine decarboxylase gene probe, investigators have shown that the ornithine decarboxylase gene may be amplified in cells that overproduce ornithine decarboxylase.[17,19] Furthermore, induction of ornithine decarboxylase has been associated with an increased amount of ornithine decarboxylase messenger RNA, suggesting the regulation of ornithine decarboxylase gene transcription or messenger RNA stability, or both, during cell proliferation.[17,19] The availability of these mammalian ornithine decarboxylase complementary DNA gene probes will facilitate studies to determine the specific role of ornithine decarboxylase during cell proliferation. These studies should allow for further understanding of the functional importance of polyamines in normal cell growth and in clinical disorders.

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Troublesome Problems and an Awesome Thought

We have just passed the midpoint of the 1980s and we have just had a presidential election. So far nothing very terrible has happened, but many might add that nothing has improved very much either. There are many troublesome problems in both medicine and society, and so far there do not seem to be any very good solutions anywhere to be found. The mood of the electorate seemed to be that as long as things are not getting any worse let's not rock the boat too much. However, the power of the liberal theories of the recent past seems to be fading, and conservative beliefs appear to be gaining some greater acceptance, with no proof that these theories will work any better than those of the liberals.

So far no social, economic or political theory or belief seems equal to the problems we face today. The Marxists do not seem to have any generally workable answer, the socialist approach has been less than satisfactory where it has been seriously tried and even this freedom-loving nation has found unfettered free enterprise to be unacceptable. While the proponents of each of these systems loudly espouse their beliefs, none of their theories seem to work well in practice, either for health care or for society as a whole. Perhaps there is something missing in all of these approaches. There may be a dimension or two that they fail to take into account.

For one thing, the full impact of burgeoning science and technology on health care and on society itself has yet to be understood and appreciated. They have already raised more technologic, social, economic and political questions than our cultural systems have answers for. They are producing change faster than our systems can adjust and creating an unbelievably complex technologic, social, economic and political interdependence among people and between peoples with which we are ill prepared to deal. And then, it is almost universally overlooked that a common thread running through all this (whether we are talking about medicine or society) is people, people who act and respond in terms of their human nature and their human behavior, which in turn are biologic phenomena. People behave the way they do because of their genetic programming and their acquired experience. All in all it is little wonder that the abstract conceptual theories that have been dominating our social, economic and political thinking are falling so far short of what is needed.

The thread of human nature and human behavior, and thus of medicine, clearly weaves throughout the fabric of human social, economic and political affairs. The fundamentally biologic nature of human society must eventually be recognized, as indeed has been the fundamentally biologic basis of human nature and human medicine. The problems of all are adaptation to stress and to change in their internal and external environments. When the adjustments are good there is health and well-being. When the adjustments are not good there are serious human problems—that is, problems for humans.

Medicine is the one profession that is authoritative for human behavior in health and disease. It is awesome to think of the quantum leap that will be necessary if the expertise in medicine and human biology that is needed is to be developed, and then brought to bear, to help deal with the complex social, economic and political human problems that are being so rapidly created, and even compounded, by the new science and technology. It seems likely that the thread of medicine will soon be found to weave throughout the fabric of human society in ways we have never yet considered. Maybe the doctor glut is nature's way of preparing the medical profession for some new responsibilities that may lie ahead!

MSMW

Case Reports

Acute Hepatitis Associated With Colorado Tick Fever

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COLORADO TICK FEVER is an acute viral illness transmitted by bite of the wood tick *Dermacentor andersoni*. After an incubation period of from three to six days, chills, severe headaches, photophobia, myalgias, fever and leukopenia develop, lasting from five to eight days. Many patients experience a biphasic illness referred to as "saddle-back" fever. The initial symptoms may abate for one to two days, only to be followed by a recurrence of these symptoms for another two to four days before they subside. Although Colorado tick fever usually has a benign course and an excellent prognosis, in a few cases complications have been described, especially in children, of encephalitis, aseptic meningitis and hemorrhage.[1,2] Other associated syndromes have been pericarditis,[3] epididymo-orchitis, rheumatic fever syndrome and atypical pneumonitis.[4] In this case report the association of hepatitis with Colorado tick fever is described.

Report of a Case

A 67-year-old women presented in May 1983 with severe headaches, photophobia, myalgia, feverishness and chills for the past 24 hours. Three days before she had removed an attached wood tick. On examination she had conjunctival injection but no rash or fever. Her leukocyte count was 5,100 per μl with 75% segmented and 7% band forms. The presumptive diagnosis was Colorado tick fever, but because of the possibility of Rocky Mountain spotted fever, she received tetracycline, 500 mg, every six hours. Three days later she was admitted to hospital for supportive care because of increasingly severe symptoms and weakness. She said she had not taken aspirin, acetaminophen or medications other than tetracycline. She had had no exposure to blood products or persons with hepatitis. In the past she had had cholecystectomy.

Examination findings were unchanged from before, except for a temperature of 38.2°C (100.8°F). The following day her leukocyte count was 1,300 per μl with 38% segmented forms, 22% bands and 40% lymphocytes. Analysis of urine and chest x-ray film showed no abnormalities. Her serum aspartate aminotransferase level (glutamic oxaloacetic transaminase [SGOT]) was 204 units per liter (normal, 7 to 24); alkaline phosphatase, 87 units per liter (normal, 18 to 61); γ-glutamyl transferase (GGT), 234 units per liter (normal, 5 to 30), and bilirubin, 0.45 mg per dl (normal, 0.3 to 1.5). Blood cultures were negative for bacterial pathogens.

(Loge RV: Acute hepatitis associated with Colorado tick fever. West J Med 1985 Jan; 142:91-92)

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The tetracycline regimen was stopped. When her symptoms and fever resolved with supportive care over two days, she was discharged. Except for weakness, she felt well for five days, when right upper quadrant abdominal pain developed. When readmitted to hospital she was afebrile, but her liver edge was tender and palpable at the costochondral junction. There was no icterus. Laboratory values were as follows: hemoglobin, 15.0 grams per dl; leukocyte count, 7,100 per μl with 60% segmented forms, 2% bands and 38% lymphocytes; SGOT, 300 units per liter; serum alanine aminotransferase (glutamic pyruvic transaminase [SGPT]), 484 units per liter (normal, 4 to 25); GGT, 666 units per liter, and bilirubin, 0.9 mg per dl. The serum amylase level remained normal. A liver ultrasound study showed no biliary duct dilation. Tests for hepatitis B surface antigen, hepatitis B core antibody and hepatitis A virus antibody were negative. *Proteus* OX-19 agglutinins were negative and *Proteus* OX-K was 1:80. Serologic tests for brucellosis, leptospirosis, Q fever, Epstein-Barr virus and influenza A and B were negative. Cytomegalovirus titers and cultures were negative. Rocky Mountain spotted fever acute and convalescent titers were 64. Serologic test for acute Colorado tick fever by immunofluorescence antibody was less than 64, and convalescent titers were 2,048 or higher.

After two days her symptoms spontaneously resolved and SGOT, SGPT and GGT levels dropped to 78, 219 and 462 units per liter, respectively. Her recovery was uneventful, and all the enzyme values returned to normal within four weeks.

Discussion

This patient's clinical course was typical of Colorado tick fever except for the lack of "saddle-back" fever, which may be absent in as many as 52% to 58% of patients.[2,5] The diagnosis was confirmed by seroconversion of Colorado tick fever antibody. Other possible causes of hepatic inflammation were excluded. Although she received a short course of tetracycline by mouth, this drug is an uncommon cause of hepatic injury. When seen, tetracycline produces cholestatic features unlike the hepatocellular injury pattern seen in this patient.

In two extensive case reviews of the clinical and laboratory aspects of Colorado tick fever, hepatitis or abnormal liver function was not specifically sought.[2,4] In their review of 115 cases, Spruance and Bailey mentioned one child with Colorado tick fever-associated encephalitis and high-titer cold agglutinins who also had icterus and elevated SGOT levels.[2] Goodpasture and co-workers reported abdominal pain and vomiting occurring in about 20% of patients.[4] Hepatitis may have been present in some of these patients.

In the present case, hepatitis followed the initial acute phase of the illness. When Goodpasture and colleagues reported syndromes of epididymo-orchitis, rheumatic fever-like illness and atypical pneumonitis, they suggested that "circulating immune complexes may be the cause of the second phase of illness that many patients experience, as well as some of the unusual manifestations of the disease."[4] Per-

haps the hepatitis in this patient may have been an immune complex manifestation.

There is little pathologic information about Colorado tick fever because human fatalities are rare. The virus is easily isolated from erythrocytes of most affected patients and from cerebrospinal fluid of those with central nervous system involvement. Viral replication occurs in bone marrow, lymph nodes, spleen, lungs, heart and liver of rhesus monkeys but without histologic abnormalities.[6] Identifying the virus in liver biopsy specimens or serum immune complex assays in future patients who have Colorado tick fever and evidence of hepatic dysfunction could determine if this association is primarily infectious or immunologic.

Colorado tick fever is a frequent disease in the mountainous western regions of the United States. More than 2,500 cases have been reported in the Rocky Mountain states in the past ten years, but the actual incidence is probably significantly higher (State Departments of Health of Montana, Idaho, Utah, Wyoming, Colorado and New Mexico, written communications, November 1983). With summer tourists returning home from endemic areas, this infectious disease can be seen nationwide.[4,7] Physicians should be alert to the possibility of hepatitis as an unusual manifestation of Colorado tick fever.

Addendum

Since submission of this manuscript, another patient was seen in whom serologically confirmed Colorado tick fever was complicated by thrombocytopenia (58,000 per μl), neutropenia (900 per μl) and elevated SGOT (42 units per liter) during the second phase of his biphasic illness. Analysis of serum immune complexes by Clq binding assay was normal (2 μg per ml). His recovery was uneventful.

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Cosyntropin Stimulation in Adrenal Vein Testing for Aldosteronoma

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ONCE A DIAGNOSIS of primary aldosteronism is established, it is necessary to distinguish between adenoma and hyperplasia. Aldosteronomas, comprising one half to two thirds of cases, are almost always unilateral. Surgical excision generally cures or improves the hypertension while preserving adrenal function. Hyperplasia is almost always bilateral. Even bilateral adrenalectomy usually fails to cure the associated hypertension, so that additional treatment is needed. Methods for identifying and localizing aldosteronomas include adrenal venography,[1-7] computed tomography,[1,8-12] adrenal isotopic scanning[1-3,13-17] and hormonal sampling via adrenal vein catheterization.[1-7,12,18] Adrenal venograms involve a risk of serious complications, including adrenal infarction and retroperitoneal hemorrhage. Computed tomographic (CT) scans and radioisotopic adrenal scanning fail to detect small aldosteronomas and occasionally produce false-positive results. The exact role of these two noninvasive tests remains to be defined. Adrenal venous sampling, with over 90% sensitivity,[1,12] sets the standard. Even this test, however, is subject to occasional error caused by episodic secretion of aldosterone.[18] To overcome this shortcoming, multiple sampling[18] and adrenocorticotropic hormone (ACTH)-stimulated sampling[1,3] have recently been advocated. The latter technique, the simpler and cheaper of the two, has not been directly compared with the standard technique of unstimulated adrenal vein sampling. The following case of primary aldosteronism, in which results of both the computerized tomographic scan and unstimulated adrenal vein sampling were inconclusive, documents the increased sensitivity of cosyntropin-stimulated adrenal vein sampling.

(Noth RH, Glaser SL, Palmaz JC: Cosyntropin stimulation in adrenal vein testing for aldosteronoma. West J Med 1985 Jan; 142:92-94)

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Report of a Case

A 56-year-old man with chronic alcoholism was referred in February 1981 for evaluation of hypertension, hypokalemia and a 1-cm right adrenal mass seen on a CT scan. Mild hypertension was first noted in this patient in 1974 and diuretic therapy begun. Intermittent mild hypokalemia was attributed to his alcoholism and diuretic therapy. Cirrhosis of the liver was documented by liver biopsy three years before referral. The patient had been taking spironolactone (Aldactone)—150 mg a day—since one year before referral.

At admission, the patient's blood pressure was 135/90 mm of mercury with no orthostatic changes. Funduscopic examination showed arteriolar narrowing and mild arteriovenous nicking. The liver was slightly enlarged but not tender to the touch. No edema or ascites was present.

Results of routine laboratory studies showed normal values except for serum creatinine, 1.9 mg per dl (normal 0.7 to 1.4 mg per dl) and alkaline phosphatase, 141 units per liter (normal 35 to 115 U per liter). Serum potassium was 3.8 mEq per liter (normal 3.5 to 5.0 mEq per liter). Results of urinalysis were normal except for 1+ (10 mg per dl) protein. Administration of spironolactone was discontinued and a 200-mEq high-sodium diet begun. Primary hyperaldosteronism was diagnosed based on the following results obtained between days 12 and 14 of the high-sodium diet: (1) renal potassium wasting (60 to 66 mEq per 24 hours) despite the development of hypokalemia (2.7 to 3.1 mEq per liter); (2)

ABBREVIATIONS USED IN TEXT
ACTH = adrenocorticotropic hormone
CT = computed tomography
PA = plasma aldosterone

urinary aldosterone excretion, 25 μg every 24 hours (normal 2 to 12 μg per 24 hours on a 200-mEq sodium diet); (3) an 8 AM supine plasma aldosterone (PA) level of 22 to 30 ng per dl (normal less than 10 ng per dl) despite suppressed supine and ambulatory plasma renin activity in the 0.1 to 0.3 ng per ml per hour range (normal 0.9 to 4.5 ng per ml per hour for patients on a 100- to 200-mEq sodium diet) and (4) a supine PA level of 16 ng per dl (normal less than 10 ng per dl) following intravenous infusion of 2 liters of normal saline solution over four hours. Plasma aldosterone levels obtained from blood drawn at noon (7 ng per dl) after four hours of ambulation were lower than levels at 8 AM after 10 hours supine (26 ng per dl). At 7 AM, eight hours after administration of 1 mg of dexamethasone, the plasma cortisol value was 3.6 μg per dl (normal less than 5 μg per dl). Urinary catecholamines were 13 μg each 24 hours (normal less than 100 μg); 17-ketosteroids were 5 mg every 24 hours (normal 9 to 22 mg every 24 hours). Mean preoperative blood pressure based on the 23 values obtained between weeks 2 and 3 of the high-sodium diet was 150/92 ± 16/9 mm of mercury (standard deviation).

The CT scan showed a 1.3-cm focal enlargement of the right adrenal (Figure 1, upper). An area of irregularity in the posterolateral limb of the left adrenal (Figure 1, lower) made interpretation of the CT scan equivocal. To evaluate the functional status of the left adrenal, selective hormonal sampling of the adrenal vein was done with and without stimulation by the synthetic ACTH analog cosyntropin (Cortrosyn), four weeks after discontinuing spironolactone. The 200-mEq sodium diet had been continued, supplemented by 40 to 120 mEq potassium a day to maintain the serum potassium at about 3.5 mEq per liter. Results are summarized in Table 1. The baseline set of adrenal vein values is equivocal. Adrenal vein aldosterone is in fact slightly higher on the involved right side. However, the higher aldosterone-to-cortisol ratio on the left suggests a left-sided lesion. Bilateral aldosterone secretion is also compatible with hyperplasia or bilateral adenomas. The postcosyntropin set of values is unequivocal. Aldosterone rises over 400-fold on the involved right side while remaining at the mixed venous level on the left. The marked rise in cortisol on the left positively identifies successful recatheterization in the left adrenal vein.

Following the adrenal vein sampling, administration of spironolactone was restarted in preparation for surgical operation a month later. Right adrenalectomy was carried out via a right posterior flank incision. A benign 1.4-cm orange cortical adenoma was found on gross pathological examination. Microscopic examination showed a benign cortical adenoma. Platelike cristae in mitochondria and spironolactone bodies were identified by electron microscopy. The remaining right adrenal cortex showed mild clear cell hyperplasia involving cells in the zona glomerulosa, fasciculata and reticularis. One week following operation, serum potassium increased to 5.6 to 5.9 mEq per liter. At noon, after four hours of ambulation, the plasma aldosterone level was 3 ng per dl and urinary aldosterone excretion was less than 1 μg every 24 hours. Plasma cortisol was 19 μg per dl at 8 AM. Mean postoperative blood pressure, based on the 15 values from the second postoperative week, was 126/81 ± 10/9 mm of mercury (standard deviation). Fludrocortisone therapy was subsequently begun and continued for two months. One year later, the patient was normotensive and normokalemic, off all medication.

Assays for plasma renin activity, plasma and urinary aldosterone, urinary 17-ketosteroids and urinary catecholamines were done by Upjohn Diagnostic Laboratories.

Comment

Cosyntropin-stimulated adrenal vein sampling offers two advantages over the customary unstimulated sampling procedure. First, it provides a highly reliable marker for adrenal vein blood by continuously stimulating cortisol secretion. In the present case, baseline cortisol secretion was adequate to serve as a marker. However, in the absence of cosyntropin, when neither the aldosterone nor the cortisol level in the adrenal vein is higher than mixed venous levels, ambiguity arises. This circumstance occurred in 4 of the 17 cases reported in the literature in which complete aldosterone and cortisol data were available for review.[1,4,6,18] In such a situation, either aldosterone secretion is suppressed, an aldosterone secretory episode has been missed or the sample is not

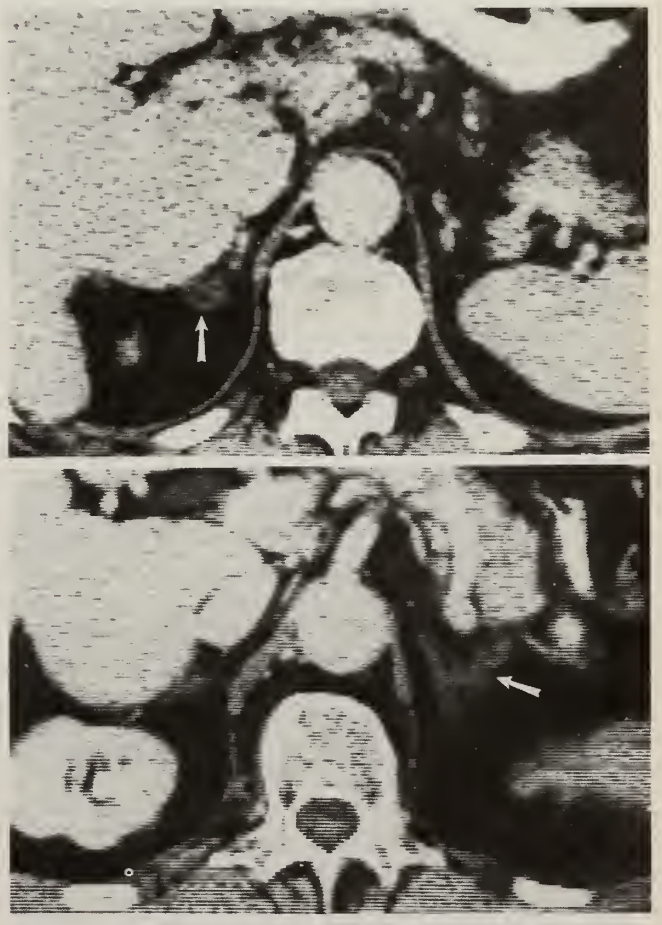

Figure 1.—Abdominal CT scans: **Top**, At the T12-L1 level, the rounded area of low attenuation (**arrow**) attached to the posterolateral limb of the right adrenal represents the 1.3-cm adenoma. **Bottom**, At the L1 level, the posterolateral limb of the left adrenal (**arrow**) is irregular in outline, compatible with either an adrenal mass or superimposed retroperitoneal vein.

TABLE 1.—*Selective Adrenal Vein Catheterization in a Patient With Primary Aldosteronism*

Site	*Time (AM)*	*Plasma Aldosterone (ng/dl)*	*Plasma Cortisol (μg/dl)*	*Plasma Aldosterone/ Plasma Cortisol*
Inferior vena cava*	9:08	26	7.0	3.7
Left adrenal	9:32	57	27.3	2.1
Right adrenal	10:10	72	104.0	0.7
Cosyntropin bolus†	10:18	—	—	—
Right adrenal	10:44	30,700	1,710.0	17.9
Left adrenal	10:55	119	540.0	0.2
Inferior vena cava*	11:10	125	22.9	5.5

* Inferior vena cava below adrenal veins.
† 250-mg IV bolus of cosyntropin.
Plasma renin activity at 9:08 AM was 0.1 ng per ml per hour; serum potassium was 3.4 mEq per liter. The catheter remained in the right adrenal vein between 10:10 and 10:44 AM.

adrenal blood. Even radiographic localization of the catheter by injection of small amounts of contrast medium at the time of sampling cannot provide conclusive results because catheters can move and adrenal blood can become diluted. A second advantage of cosyntropin stimulation, the one illustrated by the case, is selective enhancement of aldosterone secretion by adenomas. Aldosterone secretion by adenomas is usually partially ACTH dependent. Plasma aldosterone follows the diurnal pattern of plasma cortisol in approximately three fourths of patients with unilateral adenoma.[1,12,17,19,20] ACTH infusion increases PA and dexamethasone partially decreases PA in the majority of patients with adenomas.[19,20] Therefore, cosyntropin stimulation should increase the sensitivity of adrenal vein sampling both by eliminating nonsecretory periods and by maximizing the magnitude of aldosterone secretion. In fact, using this technique, Weinberger and co-workers found no false-negative tests in 30 patients with unilateral adenomas identified surgically, but made no comparison with results of conventional nonstimulated testing. The present case makes this comparison and provides evidence of increased sensitivity.

Potential disadvantages of cosyntropin infusion include stimulation of aldosterone secretion from the suppressed contralateral adrenal in a patient with a unilateral adenoma, or enhancement of a difference between two hyperplastic glands. ACTH infusion stimulates aldosterone secretion from normal[21] and hyperplastic[20] adrenals. In the present case, there was no evidence of aldosterone secretion from the suppressed adrenal after cosyntropin. Similarly, in the series of Weinberger and co-workers, secretion of aldosterone from the uninvolved adrenal was always negligible in comparison to that secreted by the adenoma.[1] In four of their eight patients with bilateral hyperplasia, however, aldosterone secretion appeared to be unilateral, falsely implying the presence of an adenoma. In these four cases, cortisol values from the "uninvolved" side were either not obtained (one case) or were close to values of the inferior vena cava (three cases). The apparent lateralization, therefore, probably resulted from failure to obtain an adequate sampling of adrenal blood. More data regarding the incidence of such false-positive tests are needed. In the meantime, it appears advantageous to obtain cosyntropin-stimulated values during adrenal vein sampling.

Whether or not the baseline unstimulated sampling is also routinely needed remains an unresolved issue. In this case, as in the previously mentioned series,[1] definitive localization was possible without it. However, in the 15% of cases in which only one adrenal vein has been sampled, the magnitude of the aldosterone response to cosyntropin might prove to be useful information. An exaggerated response, such as occurred in the present case, might serve both to confirm the adenomatous nature of the process and at the same time to effectively localize it. Quantitative data on the responsiveness of both adenomatous and hyperplastic tissue are needed before the utility of this information can be assessed.

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Acromegaly With 'Normal' Growth Hormone Levels

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ACROMEGALY is a syndrome of growth hormone excess that leads to a variety of trophic changes in the tissues of the body. Frequent clinical manifestations of acromegaly include enlargement of the hands, feet, nose and mandible, coarsening of the facial features, excessive perspiration, joint pains and paresthesias.[1] Patients with acromegaly almost always have elevations in serum growth hormone concentrations, but in an occasional patient, serum growth hormone levels are within the normal range. Additionally, radiologic examination shows enlargement of the sella turcica in most of these patients.[1]

We describe the cases of three patients with the typical clinical manifestations of acromegaly whose serum growth hormone levels were not elevated. In addition, in two of these three patients, the pituitary gland was not enlarged on radiographic examination.

Reports of Cases

CASE 1. A 49-year-old man was admitted for the treatment of schizophrenia and alcohol dependence. He had typical acromegalic facial features and on close questioning recalled increasing jaw, hat and shoe size over the prior decade. He also described typical symptoms of a bilateral carpal tunnel syndrome that had been confirmed by electromyography (EMG) at another hospital. On physical examination he had frontal bossing and prognathism. The hands and feet were moist and large with increased amounts of soft tissue. The rest of the examination showed no abnormalities. A fasting plasma glucose level was 200 mg per dl with other routine laboratory tests within normal limits. A fasting serum growth hormone level was 4 ng per ml (normal, < 10). A thyrotropin-releasing hormone (TRH) stimulation test showed a basal growth hormone level of 8.6 ng per ml, increasing to a peak of 29 ng per ml at 45 minutes. A glucose suppression test showed a serum growth hormone level of 7.9 ng per ml 60 minutes after glucose ingestion. Thyroid, adrenal, gonadal and prolactin testing was normal. Skull x-ray films showed an enlarged jaw and large frontal sinuses but the sella turcica was not enlarged. Sella turcica tomograms showed a normal sella with an anteroposterior diameter of 1.5 cm and a depth of 0.8 cm. A computed tomographic (CT) scan showed an area of low density on the right side of the pituitary, consistent with a pituitary adenoma, with no evidence of sella turcica destruction or suprasellar extension. Transsphenoidal exploration of the pituitary gland showed a 2-mm pituitary tumor, which was removed in its entirety. Postoperatively, serum growth hormone values were all less than 3 ng per ml, there was no stimulation of growth hormone secretion after administration of TRH and the symptoms of a bilateral carpal tunnel syndrome disappeared.

ABBREVIATIONS USED IN TEXT
CT = computed tomography
EMG = electromyography
TRH = thyrotropin-releasing hormone

CASE 2. A 41-year-old man, a dermatologist, sought medical attention because of the development of bilateral carpal tunnel syndrome, which was confirmed by EMG. Over the past several years he had noted coarsening of his facial features but said he had not had changes in ring or shoe size, hyperhidrosis or other symptoms associated with acromegaly. On physical examination a prominent brow and coarsening of the facial features were seen in comparison to pictures taken five years previously. His hands were enlarged with increased amounts of soft tissue and he had numbness of his thumb and first two fingers of both hands. There were no other abnormalities noted. Routine laboratory testing was within normal limits except for a fasting glucose level of 158 mg per dl. A fasting serum growth hormone level was 8 ng per ml. A glucose suppression test showed a pronounced abnormality in glucose metabolism with a 120-minute glucose concentration of 336 mg per dl. Serum growth hormone concentrations did not suppress in response to glucose ingestion (60 minutes, 9 ng per ml). Serum growth hormone levels did not increase in response to administration of TRH (0 minutes, 8, 15 minutes, 9, 30 minutes, 8, and 60 minutes, 10 ng per ml). Somatomedin levels were elevated at 5.7 units per ml (0.5 to 2.0 units per ml is the normal range). Thyroid, adrenal, gonadal and prolactin testing was normal. Lateral skull x-ray films did not show an enlarged sella turcica. On CT scan of the pituitary gland there was a radiolucent area measuring 6 mm in diameter, consistent with a pituitary adenoma. The patient's sella turcica was explored via the transsphenoidal approach and a pituitary microadenoma was removed uneventfully. Postoperatively, several serum growth hormone levels were less than 5 ng per ml, and his bilateral carpal tunnel syndromes rapidly resolved.

CASE 3.* The patient, a 56-year-old man, was admitted with a chief complaint of enlargement of his hands and feet that began about 14 years before admission. In addition, he noted increased perspiration with offensive body odor, progressive numbness and weakness in both hands, enlargement of his tongue and mild coarsening of his facial features. On physical examination he had a slightly elevated blood pressure of 150/90 mm of mercury, minimal coarsening of his facial features, an enlarged tongue that filled most of his oropharynx, enlarged hands and feet with increased soft tissue hypertrophy and numbness in the thumb and first two fingers of both hands. Routine laboratory tests were normal. Numerous growth hormone levels were measured that were all less than 10 ng per ml. The serum growth hormone response to insulin hypoglycemia and glucose suppression was normal but the response to both levodopa and TRH administration was abnormal (TRH at 0 minute, 4.2, and 15 minutes, 17.5 ng per ml; levodopa at 0 minute, 7.7, and 60 minutes, 2.1 ng per ml). The somatomedin levels were raised at 2.5 units per

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Submitted, revised, 29, 1983.

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* This case has been reported previously in the *Journal of Neurosurgery* 1979; 50:503-507.

ml. Lateral skull x-ray films showed an enlarged sella turcica with bulging of the anterior and inferior portions. A pneumoencephalogram showed no evidence of suprasellar extension. The sella turcica was explored via the transsphenoidal approach and an enlarged but grossly normal pituitary gland was exposed. No adenomas were located during careful exploration. Histologic examination of pituitary biopsy specimens failed to show either adenomatous changes or an increase in granulated acidophils. Postoperatively, there was a subjective resolution of symptoms but results of physical examination and repeat laboratory testing of growth hormone dynamics and somatomedin levels were unchanged.

Methods

Growth hormone levels were measured by radioimmunoassay by either Smith Kline & French Laboratories or Consolidated Biomedical Laboratories, a subsidiary of Rohm and Haas Company. The normal growth hormone range in men is 0 to 10 ng per ml. Somatomedins were measured by E. Martin Spencer, MD, by an assay that used human placental membrane as the receptor and radiolabeled somatomedin A purified from human plasma as the ligand. This assay detects somatomedin A and C and the normal level for men is 0.5 to 2.0 units per ml.[2]

Glucose suppression testing was carried out by having the patients fast overnight and then ingest one bottle of glucola (75 grams of glucose). Specimens for growth hormone determinations were obtained at 0 and 60 minutes. Levodopa stimulation consisted of the oral administration of 500 mg of levodopa after an overnight fast. Serum specimens were taken for growth hormone determination at 0, 60 and 90 minutes. The TRH testing consisted of the intravenous administration of 200 μg of TRH with blood specimens for growth hormone determinations taken at 15-minute intervals for one hour.

Discussion

The three patients described in this report all presented with the typical clinical manifestations of acromegaly but in all three cases the serum growth hormone values were within the "normal" range. Over the past decade at our institution, which is *not* a major referral hospital for pituitary tumors, we have diagnosed acromegaly in nine patients. Thus, a third of the patients with acromegaly diagnosed at this hospital in the past decade have had growth hormone levels within the "normal" range. This frequency of acromegaly with "normal" growth hormone levels is considerably higher than that reported in the literature. The incidence of acromegalic patients with "normal" growth hormone concentrations varies from study to study (Table 1), with an average incidence of 4.9% if one combines these series.[3-21]

There are several possible explanations for the high incidence of acromegalic patients with "normal" growth hormone concentrations seen at our institution. First, our hospital is not a major referral center for the treatment of acromegaly or pituitary tumors and, therefore, this incidence of "normal" growth hormone acromegaly is not biased by the referral of only patients with clearly documented disease. It is likely that patients with "normal" hormone values and possible acromegaly are not referred to major centers for definitive diagnosis and treatment. This selection bias would result in an artifactually reduced incidence of acromegaly with "normal" growth hormone levels reported by these major centers.

TABLE 1.—*Number of Untreated Cases of Acromegaly With Growth Hormone Levels < 10 mg/dl Divided by Total Number of Untreated Cases*

Source		*Percent*
Lawrence et al, 1971[3]	0/12	0
Mims and Bethune, 1974[4]	5/62	8
Levin et al, 1974[5]	7/50	14
Williams et al, 1975[6]	4/68	6
Becker et al, 1974[7]	1/12	8
Pelkonen and Grahne, 1975[8]	1/25	4
Atkinson et al, 1975[9]	0/10	0
Giovanelli et al, 1976[10]	0/29	0
Decker et al, 1976[11]	0/14	0
Hoi et al, 1977[12]	2/51	4
Milam et al, 1977[13]	0/16	0
Clemmons et al, 1979[14]	5/57	9
Law et al, 1979[15]	8/74	11
Tucker et al, 1980[16]	1/22	5
Baha et al, 1980[17]	2/28	7
Lindholm et al, 1981[18]	0/14	0
Richards and Thomas, 1980[19]	0/34	0
Schuster et al, 1981[20]	0/11	0
Teasdale et al, 1982[21]	0/56	0
Jadrevic et al, 1982[22]	2/64	3
	38/709	5.4

Second, the medical staff at our institution is familiar with the entity of "normal" growth hormone acromegaly and will, in spite of "normal" growth hormone levels, aggressively pursue the diagnosis of acromegaly in a patient with the appropriate clinical manifestations.

Third, all three cases were diagnosed since 1978 and, in fact, two of the three patients were diagnosed in 1982. Clearly, in recent years several new diagnostic procedures have become available that greatly aid in the diagnosis of pituitary tumors and acromegaly, in particular. A firm diagnosis of acromegaly was probably reached in some of our cases only because of the availability of CT scanning, somatomedin assays[14,23] and TRH stimulation tests.[24,25] Last, the number of cases of acromegaly seen at this medical center is small and therefore the high incidence of "normal" growth hormone acromegaly could be due to chance.

The mechanism by which acromegaly occurs despite "normal" growth hormone levels is unknown. Mims and Bethune have described in detail five cases of patients with acromegaly who have had normal basal growth hormone levels but whose growth hormone response failed to decrease during hyperglycemia or increase after levodopa administration, hypoglycemia, stress and sleep.[4] These authors postulated that fixed tumor production of high-normal levels of growth hormone could cause the signs and symptoms of acromegaly. Our three patients similarly showed abnormalities of growth response to various manipulations and, therefore, would support this hypothesis. It should be recognized that the presence of "normal" basal growth hormone levels does not rule out the possibility that these patients have intermittently elevated growth hormone levels. In fact, Cryer and Daughaday have reported several acromegalic patients with "normal" fasting growth hormone levels who, on continuous monitoring, had spikes of growth hormone secretion to very high levels.[26] It is possible that bursts of growth hormone release could have been undetected in our acromegalic pa-

tients and that these intermittent elevations in growth hormone concentration are enough to induce the abnormalities associated with acromegaly. Additionally, it is now recognized that human growth hormone is a complex of structurally different proteins with varying biologic activity.[27] It is possible that in our patients with "normal" growth hormone acromegaly the radioimmunoassay used failed to detect biologically active growth hormone.[28] However, it should be recognized that in most patients with acromegaly the radioimmunoassay of growth hormone has been shown to yield higher circulating levels than do biologic radioreceptor assays.[29] Occasionally, the clinical and radiologic findings of acromegaly in association with "normal" growth concentrations is due to "burnt out" acromegaly. This is not likely in our cases because our patients had the symptoms of acromegaly which resolved after surgical treatment and, on exploration of the pituitary, no evidence of infarction or hemorrhage into an adenoma was noted.

Last, readers should know that the absolute elevation in radioimmunoassayable growth hormone correlates poorly with the severity of the clinical syndromes of acromegaly.[14,30] Some investigators have reported that somatomedin levels, the putative mediator of the growth-promoting action of growth hormone, are a better reflection of disease activity.[14,23,31] In two of our patients in whom somatomedin levels were measured, they were elevated. Additionally, others have described cases of acromegaly with increased somatomedin levels and "normal" growth hormone concentrations.[14] It is possible that through a variety of mechanisms, elevations of somatomedin levels could occur in patients with "normal" growth hormone levels and thus result in the clinical manifestations of acromegaly.

Another interesting feature of our cases is that two of our three patients had acromegaly in the absence of an enlargement of the pituitary gland on radiographic examination. Similarly, two of the five patients with "normal" growth hormone acromegaly described in detail by Mims and Bethune also had normal-sized sellae.[4] The incidence of acromegaly in patients with a normal sella turcica on radiographic examination varies greatly from study to study, but, in general, the vast majority (more than 90%) of acromegalic patients have an enlarged sella turcica.[1,8,10,14,20,22] In two of our cases, a microadenoma was described both on CT scan and on pituitary exploration. It is tempting to postulate that the "normal" growth hormone levels and the presence of a microadenoma signify early disease, but both of our patients had the signs and symptoms of acromegaly for several years before diagnosis.

Based on our experience, it is important that clinicians recognize that acromegaly need not be associated with either elevations in basal growth hormone levels or radiographic enlargement of the pituitary gland. Clearly, if clinical findings suggest acromegaly, a "normal" basal growth hormone level or a normal sella turcica size on radiographic examination (or both) should not deter a physician from pursuing a diagnosis of acromegaly. There are several diagnostic tests that were helpful in confirming a diagnosis of acromegaly in our patients. These include a rise in serum growth hormone levels in response to TRH administration, failure of serum growth hormone concentrations to suppress below 5 ng per ml after glucose ingestion, and elevation in somatomedin levels and the presence of a pituitary microadenoma on a CT scan. Patients in whom the clinical diagnosis of acromegaly is suspected but not supported by basal growth hormone levels or routine x-ray films should have some or all of these diagnostic studies.

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Correspondence

The Editorial Board will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words, and must be typewritten, double-spaced and submitted in duplicate (the original typescript and one copy). Authors will be given an opportunity to review any substantial editing or abridgement before publication.

Treatment of Mild Hypertension

TO THE EDITOR: I appreciate very much the publication of the editorial by Feigal and Hulley[1] which comments on my paper, "Hypertension—Indications, Goals, and Potential Risks of Drug Therapy."[2] I wish to respond to some of their comments.

Feigal and Hulley cite the Hypertension Detection and Follow-up Program (HDFP) report[3] that the development of left ventricular hypertrophy was more frequent in *referred care* (RC) subjects than in *stepped care* (SC) subjects. HDFP compares intensive care including a strong support system with routine care. It is not a study of drug versus placebo. It does not prove that differences in outcome were due to the presence or absence of drug therapy.

Feigal and Hulley also cite the USPHS Study of Mild Hypertension,[4] which did show that left ventricular hypertrophy developed in more placebo-treated subjects than in drug-treated subjects. However, we should remember that diastolic pressure was permitted to range as high as 130 mm of mercury over the eight-year follow-up period. I have suggested that drug treatment be started if diastolic pressure is consistently greater than 105 mm of mercury despite hygienic measures of treatment.

The reduction of coronary heart disease mortality reported in the Australian Therapeutic Trial in Mild Hypertension[5] is not valid because the study was not double-blind. Subtle but important influences on the physician-patient relationship may occur in such a study. This is illustrated by the fact that more drug-treated subjects than control subjects received two or three drugs. One would expect that more control subjects would be given a placebo for second and third step drugs since their blood pressure would be more likely to be above goal. In addition, active drug-treated subjects made more visits than placebo-treated subjects. This, also, is contrary to what would be expected.

While the Multiple Risk Factor Intervention Trial (MRFIT)[6] showed an increased coronary heart disease death rate in intensively treated hypertensive (S1) subjects with electrocardiographic findings on entry, this does not appear to be the complete explanation. Subjects with the lowest entry blood pressure (diastolic 90 to 94 mm of mercury) and, hence, the lowest treatment goal blood pressures had an increased coronary heart disease death rate. It does not seem likely that these subjects would have a greater frequency of abnormal findings on entry electrocardiograms.

Feigal and Hulley comment that my paper fails to address the fact that the low disease event rate (complication rate) and the low statistical power of the studies may account for the apparent lack of efficacy of drug treatment in the VA and USPHS studies. I believe that the burden of proof lies with those who suggest that mild hypertension should be treated with drugs. If we design studies to determine if drug treatment has a favorable effect on morbidity and mortality of hypertension and we find no significant difference, we should not advocate drug treatment.

Feigal and Hulley state that patients older than 50 years are at greater risk and therefore should be given drug therapy. Kirkendall and Hammond[7] reviewed the data of the VA Study of Mild to Moderate Hypertension and concluded that there was no evidence that drug treatment was more effective in older subjects with entry diastolic pressures of 90 to 104 mm of mercury.

Unfortunately, the recent report of the Joint National Committee for the Detection and Treatment of Hypertension[8] continues the error of citing the HDFP study to support their recommendations. This is not valid for reasons given above and in my paper.

Evidence now available from properly designed studies suggests that drug treatment of mild hypertension (diastolic 90 to 105 mm of mercury) does not significantly reduce manifestations of coronary heart disease in particular, nor morbidity and mortality in general. In addition, we now have data that suggest that drug treatment of mild hypertension may increase the coronary heart disease death rate. Therefore, it is suggested that hygienic measures of treatment should be initiated and maintained in cases of mild hypertension and that drug therapy should be prescribed if diastolic pressure is consistently greater than 105mm of mercury.

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Patient Compliance in Drug Therapy for Hypertension

To the Editor: I am writing in regard to Dr G. N. Aagaard's article on drug therapy for hypertension.[1]

I fully agree it is dangerous to lower blood pressure abruptly, indiscriminately or erratically—especially the latter. Patients who do not accept the idea that blood pressure medication is an on-time-as-directed type of therapy should not be treated. Physicians who will not keep calendar count of refills should not treat hypertension.

The only study that reflects this thinking is the HDFP (Hypertension Detection and Follow-up Program). But the journal's article misses the reason for the different mortality rates in the HDFP study. The author theorizes, "It is possible that the strong psychological and social support given the SC [stepped care] subjects over the five-year study caused the reduction in mortality." The difference between the stepped care and referred care subjects was *compliance*. In this study, compliance was drummed into those patients in the stepped care group only.

The findings I have most faith in are from the combined insurance company study of 20,000 deceased hypertensive patients who were under treatment at the time of death, evaluated from an actuarial point of view. This study came up with the conclusion that the lower the blood pressure, the longer the life span. It did not deal with lowering the blood pressure per se unless the insured died while the pressure was being lowered.

To get the mortality down to 2% to 4% greater than normotensive insured men, the systolic pressure had to be reduced to 137 mm of mercury or less and the diastolic to 73 mm of mercury or less. Curiously, when these two numbers are added together, they total 210 or 2° less than the boiling point of water at sea level in degrees Fahrenheit. This coincidence makes it easy for patients to remember.

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REFERENCE

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Presumed Chlamydial Infections and Treatment of Sexual Partners

To the Editor: In his discussion of *Chlamydia trachomatis* infections,[1] Martin Quan does a good job of summarizing the clinical features, varied presentations and high incidence. He points out that many practicing physicians, due to the expense and trouble of culturing for *Chlamydia*, will treat presumed chlamydial infections empirically. I thoroughly agree with this. However, he does not touch on an important corollary which is that sexual partners likewise should be treated.

This particular aspect of treating sexually transmitted diseases continues to be a matter of frustration for me. Often, partners of my patients will see another physician who, after a gonorrhea culture is done and found to be negative, will tell that patient that he or she has no sexually transmitted disease. I feel that treating sexual partners is very important and the above scenario makes both the other physician and myself look foolish. I believe that we physicians should be consistent in treating sexual partners of persons presumably infected with *Chlamydia*.

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Skin Testing During Pregnancy

To the Editor: This letter is in response to the epitome "The Radioallergosorbent Test" in the October 1984 issue.

The authors state, "it is generally agreed that skin testing is contraindicated during pregnancy and that RAST [radioallergosorbent test] is an acceptable alternative."

I disagree with this statement. It has been shown in several studies that in general immunotherapy is not contraindicated during pregnancy. Skin tests, if properly performed using scratch or puncture prior to an intradermal test and using the forearms versus the back, run a much smaller risk than immunotherapy; therefore, I do not feel they are contraindicated during pregnancy. It is assumed that an informed consent form has been carefully reviewed with the patient and that medication and equipment are available in case a reaction does occur.

Other than for the possible medical-legal aspects if a reaction does occur, I would be interested in hearing if the authors know of any medical contraindication to the testing during pregnancy.

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* * *

Drs Asser and Hamburger Reply

To the Editor: We know of no medical or biologic contraindication to skin testing during pregnancy. The reasons for that statement in our epitome are the following:

1. Most allergists will not begin immunotherapy injections during pregnancy and therefore postpone skin testing. If a pregnant patient's history suggests that her illness is due to environmental allergens that could be removed with benefit to the patient, the RAST is preferred for confirmation of the clinical impression.

2. Skin testing or immunotherapy injections with their attendant risks of anaphylactic or psychalgic reactions (or both) followed by abortion, miscarriage or the birth of a malformed infant add unnecessary malpractice risk to the practice of allergy.

The precautions Dr Harwell outlines in his letter are those generally applicable to all allergy patients but would not be adequate during pregnancy. We therefore believe

that the risk-benefit ratio is not favorable to skin testing or beginning immunotherapy injections during pregnancy. Continuing immunotherapy, when a stable safe dosage regimen has been established, is generally accepted during pregnancy.

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Recovery of Radiolabeled-Insulin From Parenteral Nutrient Solutions

To the Editor: With the availability of essential amino acids for parenteral use, an increasing number of patients are receiving total parenteral nutrition. Frequently, these patients need exogenous insulin. This can be given either by a bolus injection or the insulin can be added to the parenteral nutrition fluid and given by infusion. Adsorption of insulin to solid surfaces was first described in 1951.[1] Only a few studies have been done examining the availability of insulin from parenteral nutrient solutions (PNS).[2,3] We did not find published studies examining the recovery of insulin from PNS with use of a silastic (Hickman-Evermed) catheter. So we decided to examine this under frequently encountered clinical conditions.

Methods

Twenty units of regular insulin were added to 1,000 ml of PNS (500 ml D5OW + 500 ml 8.5% amino acid solution—Travenol). Five microcuries of insulin I 125 were added to the bottle. The bottle was shaken and five 1-ml aliquots were removed directly from the bottle. Polyvinyl tubing was connected to the bottle and the solution was run at a rate of 50 ml per hour; 1-ml aliquots of the first 100 ml of effluent were collected at the end of the tubing. These aliquots and the aliquots obtained directly from the PNS bottle were counted in a gamma counter for one minute.

Radioactivity of the consecutive 1-ml aliquots collected at the end of the tubing was compared with the radioactivity of the aliquots obtained directly from the bottle (taken as 100%). Percent recovery was calculated for each consecutive milliliter and plotted on a graph by computer. Similar experiments were done with 5% dextrose in water (with polyvinyl chloride tubing) and a silastic catheter (with PNS).

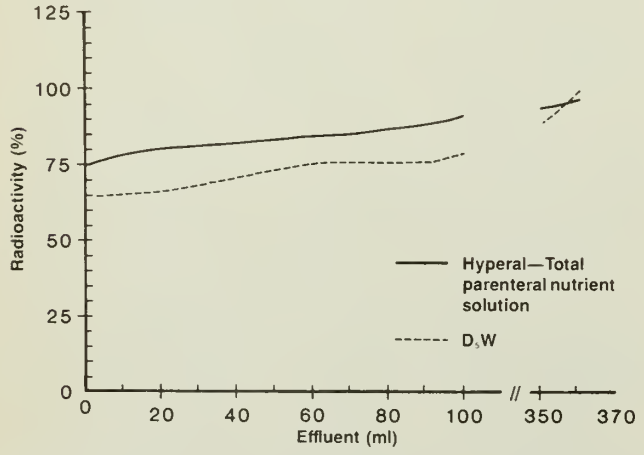

Figure 1.—Comparison of recovery of radiolabeled insulin from D5W versus parenteral nutrient solution.

Results

Recovery of the radioactivity with PNS averaged 78% by the 20th ml, gradually rising thereafter. Recovery was slightly higher with PNS than with 5% dextrose in water (Figure 1). Recovery with polyvinyl chloride tubing and silastic catheter was similar.

With common infusion rates (50 to 100 ml per hour), more than 75% recovery with a virtual plateau can be achieved in less than 20 minutes. A 50-ml washout of the infusion system to increase the recovery of insulin at the beginning of the infusion has been recommended.[4] Recovery of more than 75% of insulin within a short period of starting the infusion makes it unlikely that washout of the infusion system is critical. The expense of such a washout may be significant with these costly solutions. The use of an in-line filter significantly reduces early recovery, but it plateaus by the 20th ml as well. Absolute recovery was not measured in this study: however, the relative consistency of insulin delivery remains an important observation.*

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*This study was supported by Travenol Laboratories. The work was accepted for inclusion in the 1982 scientific section of the American Diabetes Association meeting.

Premarital Screening for Syphilis

To the Editor: I wish that I could agree with Dr Haskell's recent analysis showing that premarital screening of women for syphilis is not cost-effective.[1] If Dr Haskell's arguments are correct, then we could eliminate premarital blood testing for women entirely. The other test required premaritally—a rubella titre—has been shown to be highly insensitive (many false-negatives).[2] Furthermore, since the new rubella vaccine is highly effective[3,4] and now considered safe even for pregnant women,[4] then all we need in regard to rubella is certification of vaccination and we can be sure that our purpose in reducing chances of congenital rubella has been adequately met.

However, one of the assumptions inherent in Dr Haskell's article is a $20 office visit for each woman at a cost totaling six million dollars per annum. Since the VDRL is a screening test, a physician examination is quite simply unnecessary (and in fact is not required for men). What if the law were changed

so that the cost of VDRL screening for women was a $7 laboratory charge plus a $5 charge for blood drawing and handling? This would reduce costs by $15 per visit with no clinical loss whatsoever. Total savings would be $4.5 million, or 53% of the total assumed costs of yearly screening. Cost per case of syphilis identified would then be reduced to about $113,700 in round numbers. This is not an outrageous amount and using Dr Haskell's worst case method the screening would then appear to be cost-effective.

I would conclude, therefore, that rather than discontinue VDRL premarital screening, we should eliminate physician visits and fees which have no place in the screening procedure. I would still eliminate rubella screening and instead substitute documentation of vaccination. We could save even more money if costs for the screening were fixed. This could be accomplished by regionalizing laboratories performing screening on a competitive bid basis and either fixing clinic blood-drawing fees or similarly regionalizing sites where blood specimens for screening were to be drawn.

This seems to me to be a classical case of one potential pitfall in cost-benefit analyses—much depends on the assumptions inherent in the calculation process.

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Break Dancer's Fracture of the Fifth Metatarsal

To the Editor: Recently, break dancing has become a very popular form of entertainment in the United States. Break dancing involves expressive gestures of the head, arms and body while using steps designed to produce a fluid appearance of movement, periodically punctuated by back spins on the arched upper thoracic spine. As with any new activity, it is not surprising that previously uncommon injuries should become manifested with increased frequency. I would like to report one such break dancing-related injury.

A 17-year-old young man in good health presented to the emergency room complaining of the sudden onset of sharp pain on the lateral aspect of his right foot, which was coincident with the premature planting of this foot while performing a lateral slide step. (This is a common maneuver in break dancing, in which the undersurface of the shoe is kept just above and parallel to the floor or street while moving laterally, after which weight is gradually shifted to that foot.) On physical examination minimal swelling and moderate point tenderness were noted just proximal to the fifth metatarsal-phalangeal joint along the lateral aspect of the right foot. Ankle and foot radiographs showed a normal ankle and a spiral fracture of the distal midshaft of the fifth metatarsal.

Four types of fractures of the fifth metatarsal occur with any frequency. These include stress fractures in athletes,[1] and tuberosity and Jones's fractures[2] related to the tendinous insertion of the peroneus brevis—all three of which occur at the proximal end of the metatarsal. Fractures of the midshaft and neck are usually transverse and due to heavy objects falling on the foot.[1]

Given the position and direction of motion during the lateral slide step during break dancing, the spiral midshaft fracture suffered by this patient likely resulted from the combination of a rotational force about the long axis of the foot plus a medial load on the distal half of the metatarsal. This is similar to the direction of force in an inversion sprain of the ankle, but with a more distal focus of maximal force.

With the increasing popularity of break dancing among American youths, certain previously uncommon injuries can be expected to be seen with greater frequency, including fractures in unusual locations. Physicians should have a heightened level of suspicion when evaluating patients injured during break dancing until all associated injuries are known.

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Methods of Determining Blood Pressure

To the Editor: I read with interest the article on auscultatory blood pressure measurement by Drs Londe and Klitzner[1] in the August issue.

Although I have noticed few other people who use the technique that I use in auscultating brachial blood pressures, I personally use the bell of the stethoscope as recommended by DeGowin and DeGowin in their text *Bedside Diagnostic Examination.*[2] On page 387 of the third edition, their recommendation is "press the bell of the stethoscope lightly over the brachial artery and note the pressure read at which sounds first become audible . . . " I assume that the DeGowins presumed the findings of the study by Londe and Klitzner and therefore recommended this technique as the preferable way of eliciting blood pressures. I do not know why most people use the diaphragm of the stethoscope and would be interested in the authors' feelings about the DeGowins' method of determining blood pressures. Perhaps comparing assessment of blood pressure with a bell applied lightly to the brachial artery versus a diaphragm could be the subject of a study.

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* * *

Dr Londe Replies

To the Editor: Dr Meth raises an important question.

I have been using the bell side of the stethoscope because I was using a bell stethoscope when I began my studies in

childhood hypertension over 20 years ago. Furthermore, the sounds produced during auscultatory blood pressure measurement are heard better with the bell side.

However, sometimes the solution of one problem creates another. With little or no pressure on the bell side, there frequently is some space left between the arm surface and the stethoscope because of the irregularity of the arm surface. Consequently, the sounds are either very faint or not audible at all. Use of the diaphragm side eliminates this problem and I am now using the diaphragm side.

Dr Meth's suggestion that a study be made comparing the bell versus the diaphragm with light pressure is a pertinent one. I have tested this a few times and have found the same lowering effect on the diastolic reading when firm pressure is applied to the diaphragm side. This needs documentation with measured amounts of pressure.

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Medicare's Future

TO THE EDITOR: It was with dismay that I read your editorial entitled "Medicare—Progressively Overburdened and Underfunded" in the September 1984 issue.[1]

Your reference to Victor Fuchs's observations were both interesting and relevant to the discussion of Medicare's future. Fuchs observed that in 1935 "when the age of eligibility for social security retirement benefits was set at 65, life expectancy at age 65 was about what it is now at age 72."

Unfortunately, your editorial's ensuing support for a redefinition of old age and Medicare eligibility to age 72 overlooked several critical issues:

- In today's society, there is a tendency for people to retire earlier, making it far more difficult for the aged to pay the high cost of adequate health care. And, let us not forget that with today's retirement also comes a loss of costly private health insurance.
- Rolling Medicare eligibility back to age 72 would extract a terrible price in human suffering for those unable to pay the price of needed health care.

While an eligibility roll-back may keep Medicare solvent, it would not preserve the intent of the 1965 legislation, nor solve the underlying problems Medicare was established to address. Your references to an "emotional hue and cry" and to "special-interest groups" in speaking of the opposition to a proposed roll-back serve only to cloud these underlying issues.

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REFERENCE

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More on Pains Cured by Examination

TO THE EDITOR: Recent discussions with colleagues concerning cure of pelvic and abdominal pain through pelvic examination[1,2] have elicited another hypothesis and an intriguing case history.

The hypothesis is that partial torsion of a relatively mobile structure, such as sigmoid colon or ovary, might underlie some cases, and might be relieved after the simple manipulation inherent in examination.

The case concerns a 44-year-old internist, previously and afterwards healthy, in whom sudden, severe and unremitting right lower quadrant pain developed, which radiated to groin and vulva. Upon light abdominal palpation by a colleague, the pain remitted abruptly; urinary urgency followed, with painless passage of a stone. The apparent mechanism of pain relief was migration of a urolith, probably ureteral. The timing suggests a relationship between the events; however, the deep retroperitoneal location of the ureter should prevent effective transmission of surface pressures, especially slight ones, and alternative explanations (unrelated events, or events related by unknown means) cannot be dismissed. If several other cases were reported, the entity of "examination-assisted stone migration" might be established no matter how obscure its mechanism.

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Preoperative Evaluations

TO THE EDITOR: Levinson's report in the September issue[1] on the value of preoperative evaluations by an internist does not suggest, as Abrams concludes in the accompanying editorial, "a well-founded basis for the routine preoperative evaluation for patients undergoing eye surgery in a general community hospital."[1,2] In fact, the study is fundamentally flawed and unable to support any important conclusions regarding the question at hand.

First, whether a patient received a preoperative visit by an internist "was determined by the ophthalmologist." Consultations were performed on 258 patients, but we are told nothing specific about the cases for which consultation was not requested. Without at least minimal information regarding this group, one cannot possibly justify any conclusions regarding the value of *routine* preoperative evaluations.

Second, the benefit is questionable even in the selected patients who received a preoperative evaluation. We are told that 51/258 patients had "conditions considered important to surgical risk," but the literature cited to justify these conditions as risk factors is derived mostly from studies of patients undergoing general anesthesia for general surgery. The relevance of these supposed risks to ophthalmological surgery is unclear, especially since eye patients commonly receive only local anesthesia and mild sedation during their operations. Further, assignment of risk factors to individual patients was apparently subjective in many instances. For example, 26/59 risk factors cited were "severe chronic lung disease" or "severe asthma." No objective data are presented to justify the assessment of severity in these patients; the internists' impressions are simply taken at face value.

Even if we grant that many true risk factors were discovered, was this of any benefit to the patients? Only five actual

interventions are described, and their worth is open to debate. For example, does the attempt to "correct" severe hypokalemia over only one day before surgery really reduce perioperative morbidity? In any case, one does not establish the value of 258 consultations simply by describing a few such episodes.

Finally, even if we are convinced that benefit may derive from the discovery of the risk factors cited by Levinson, is it really necessary to call in an internist to do the sleuthing? Let us excuse the ophthalmologist for his or her presumed inability to recognize any problems residing outside the orbit, but what of the anesthesiologist? Remarkably enough, Levinson never specifies what type of anesthesia was administered (that is, local versus general), whether an anesthesiologist was present during surgery or whether a preoperative anesthesiologist's visit was made. If, as is true in many hospitals, most eye surgery patients have "local standby" anesthesia (local anesthesia with an anesthesiologist present to provide sedation, monitoring and general anesthesia should it become necessary), good anesthetic practice would require a preoperative visit. Is it not conceivable that the anesthesiologist might perceive that the patient suffers from severe lung disease, atrial fibrillation or hypokalemia? It is difficult to credit Levinson's cost-benefit analysis for the internists' consultations when the possible contribution of the anesthesiologist is entirely ignored. Dr Abrams laments the "narrow focus of specialists in medicine." Indeed.

Although Levinson has attempted to shed light on an important area of medical practice, this study unfortunately obfuscates more than it illuminates. The data fail to demonstrate the benefit of preoperative medical consultation even in her selected study population, let alone justify the conclusion put forth by both Levinson and Abrams that routine consultation in eye surgery patients over age 50 is warranted.

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* * *

Dr Levinson Replies

To the Editor: In response to comments by Dr Bryan Bohman about my article "Preoperative Evaluations by an Internist—Are They Worthwhile?", I would respond with the following.

My study was not attempting to *prove* that routine consultations by internists resulted in decreased morbidity or mortality to patients. Clearly a randomized controlled study addressing this subject would be most difficult to perform. However, in practice many ophthalmologists *do* obtain the advice of an internist before surgery and this study informs the reader about what the internists actually discovered. Objective criteria were used to evaluate risk factors including chronic lung disease whenever documentation was available and interventions were made for 39 of those 59 risk conditions. Of these surgeries, 95% were done under general anesthesia.

It is true that the anesthesiologist might have discovered and treated some of these conditions and hence the internist's help was redundant. However, overall in reviewing the number of significant risk conditions and incidental findings found by an internist, I conclude that these evaluations are warranted in patiënts older than 50 years. I suspect that appropriate interventions for risk conditions led to decreased morbidity and perhaps mortality in some cases. Furthermore, the cost of the consultation is very small relative to the cost of surgical procedures.

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* * *

Dr Abrams Replies

To the Editor: A careful reading of my comments on the Levinson article suggests that my conclusion is not as sanguine regarding Dr Levinson's thesis as Dr Bohman believes. While concurring "that routine interventions . . . should be limited only to those persons older than 50," I also go on to say that greater cost-effectiveness could have been achieved if the ophthalmologist had called for consultation in only those patients with *significant surgical risk . . . .*" In my analysis of the serious complications I stressed that only 1 of 11 major complications was even remotely affected by the internist's preoperative evaluation, and in that case (of rapid atrial fibrillation) postoperative intervention still was not necessary.

Dr Levinson's recommendation of a routine internist evaluation in patients over 50 derived from her discovery of significant risk factors present in approximately one out of five persons over 50 and the unclear nature of nonophthalmologic care of these patients. She makes the case that the costs involved were quite modest, compared with the cost of the surgery (and, presumably, anesthesia as well).

With respect to Dr Bohman's point regarding the patients in whom a consultation was not requested, one would assume that these were persons free of any overt risk after the history and physical were carried out by the ophthalmologist. These patients may have had recent clearance from their own physicians.

I still feel that Dr Levinson's contribution is worthwhile, in that it focuses on a little-addressed area in medical literature. Dr Bohman's criticisms are for the most part well taken, but I would prefer to view them in the nature of a continuing dialogue regarding the necessity for preoperative evaluations. More data are required. My editorial conclusion remains intact: "one wonders if good common sense and attention to details might not be even more cost-effective than calling internists in routinely."

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Topics in Primary Care Medicine

Hyperuricemia and Gout

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"Topics in Primary Care Medicine" presents articles on common diagnostic or therapeutic problems encountered in primary care practice. Physicians interested in contributing to the series are encouraged to contact the series' editors.

BERNARD LO, MD
STEPHEN J. McPHEE, MD
Series' Editors

Hyperuricemia and gout are frequent problems for primary care physicians. In this article the management of asymptomatic hyperuricemia and gouty arthritis are discussed.

Asymptomatic Hyperuricemia

Definition of Hyperuricemia

A serum urate level greater than 8.0 mg per dl in men or 7.0 mg per dl in women is abnormal, because these levels are statistically two standard deviations greater than the population mean. This definition is plausible physiologically because serum becomes saturated with monosodium urate at a concentration around 8 mg per dl. All urate levels in this article refer to the colorimetric method of measuring serum urate that is used in most autoanalyzers. This method is nonspecific; falsely elevated results can be caused by the presence of amino acids, uremia, high doses of vitamin C and levodopa in the test specimen. The uricase method is more specific and gives levels that are lower by 0.4 to 1.0 mg per dl than colorimetric measurements.

True elevations of serum urate can be due to the medical conditions listed in Table 1. Thus, before labeling a patient hyperuricemic, the physician should correct any reversible conditions and repeat the test that yielded an abnormal result, preferably by the uricase method.

Risks of Asymptomatic Hyperuricemia

Our assessment of the risk of asymptomatic hyperuricemia is based on several prospective studies that are flawed by the difficulty in determining how long patients had hyperuricemia before the study began. In most patients with asymptomatic hyperuricemia, symptoms never develop; some have gouty arthritis or a renal stone after many years. Tophi and gouty nephropathy rarely occur before arthritis.

The risk of *gouty arthritis* in men rose with increasing levels of serum urate in subjects of the community-based Framingham study. Gouty arthritis developed in fewer than 2% of patients with a serum urate level lower than 7.0 mg per dl during a follow-up period of 12 years. If the urate level was between 7.0 and 7.9 mg per dl, the risk of arthritis was 17%. If the urate level was between 8.0 and 8.9 mg per dl, the risk was 25%. Ten men had a urate level above 9.0 mg per dl, and in nine of them gouty arthritis developed. Only 179 women had a urate level over 6.0 mg per dl; gouty arthritis developed in 5%.

The incidence of gouty arthritis was lower in another, shorter term study. In only 3 of 69 men with a serum urate concentration greater than 9 mg per dl did gouty arthritis develop during a mean follow-up of four years. Thus, treatment to prevent gouty arthritis may be unnecessary in the short term, even for patients with high urate levels. It is not known if the natural history of hyperuricemia caused by diuretics is different. There are no data on the risk of arthritis at extremely high serum urate levels.

The risk of *renal stones* in patients with asymptomatic hyperuricemia is 3.4 stones per 1,000 patients per year, compared with 1.1 stones annually per 1,000 people without hyperuricemia.

Gouty nephropathy is rare in patients who do not have gouty arthritis, and evidence linking it with asymptomatic hyperuricemia is inconclusive. In one study, azotemia developed in fewer patients with asymptomatic hyperuricemia than in controls. It was projected that even an elevated serum urate level of 12.0 mg per dl sustained over 40 years in an asymp-

(Lo B: Hyperuricemia and gout [Topics in Primary Care Medicine]. West J Med 1985 Jan; 142:104-107)

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This work was supported in part by the Robert Wood Johnson Foundation.
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TABLE 1.—*Causes of Elevated Serum Urate Levels*

Drugs
Thiazide-related diuretics
Aspirin (less than 2 grams/day)
Alcohol
Ethambutol
Nicotinic acid
Levodopa
Decreased renal function
Acidosis
Ketosis
Lactic acidosis
Lead intoxication
Moonshine whiskey
Occupational exposure
Excessive purine production
Myeloproliferative disorders
Psoriasis

TABLE 2.—*Clinical Criteria for Primary Gout**

Maximum inflammation within one day
Redness
Involvement of the first metatarsophalangeal joint
Unilateral metatarsophalangeal joint attack
Unilateral tarsal joint attack
Oligoarthritis attack
Asymmetric swelling
Tophus
Hyperuricemia
Complete termination of an attack
More than one attack of arthritis

*Adapted from Wallace SL, Robinson H, Masi AT, et al (*Arthritis Rheum* 1977 Apr; 20:895-900).

tomatic man would increase the serum creatinine level from 1.2 mg per dl to only 2.7 mg per dl. There is no rationale for treating essential hyperuricemia to prevent the development of silent renal disease.

Although hyperuricemia is associated with coronary artery disease, it has not been shown to be an independent risk factor, and there is no evidence that lowering the serum urate level will reduce the incidence of heart disease.

Treatment of Asymptomatic Hyperuricemia

Considering its natural history, most experts recommend no treatment for asymptomatic hyperuricemia. In most patients symptoms do not develop. If gouty arthritis or a renal stone occur they can be treated readily. Little serious harm to a patient is likely if treatment to lower serum urate levels is deferred until symptoms occur.

On the other hand, the disadvantages of drugs that lower serum urate levels are substantial. The annual cost of drugs used is more than $100 per patient and side effects may be significant. The recent experience with ticrynafen, a uricosuric diuretic developed for the "problem" of thiazide-induced hyperuricemia, emphasizes the dangers of using drugs in asymptomatic patients; the drug was withdrawn because of deaths from liver disease. Moreover, compliance with medication taken for an asymptomatic condition may be poor. In decisions about asymptomatic hyperuricemia, physicians will need to explain the risks and benefits to patients, whose preferences ultimately will be decisive.

There are some situations, however, in which asymptomatic patients should be treated. Patients starting cancer chemotherapy should be given allopurinol and fluids to prevent acute uric acid renal tubular blockade. In addition, some experts recommend treating patients who have extremely high serum urate levels—that is, more than 13 mg per dl—or extremely high urine uric acid levels—greater than 1,100 mg per day—because of the projected risks of gouty arthritis or renal stones, even though there is no conclusive evidence to support this practice. If hyperuricemia is due to chronic renal failure, however, the risk of arthritis and stones is so low that prophylaxis is not indicated.

Gouty Arthritis

Clinical Presentation

The classic gouty attack is podagra; about half of first attacks involve the big toe and about 90% of patients with gout eventually have podagra. Inflammation of the first metatarsophalangeal joint, however, is not specific for gout. Diseases that mimic podagra include soft tissue infection, bunions, trauma, calcific periarthritis, ankylosing spondylitis, Reiter's syndrome, psoriatic arthritis, septic arthritis and calcium pyrophosphate deposition disease (pseudogout). Other attacks usually involve a single joint in the legs, with distal joints involved most frequently. Polyarticular attacks may occur, with asymmetric involvement of joints in the legs, sometimes sparing the foot. Attacks may be triggered by alcohol ingestion, trauma, surgical procedures, acidosis, dietary excesses, fasting and drugs that raise or lower the serum urate level.

An acute gouty attack resolves after several days or weeks, even if untreated, though resolution may be much more rapid with appropriate treatment. A total of 62% of patients have a second attack within one year, and 78% have one within two years; 7% do not experience another gouty attack for more than ten years, however.

Evaluation

The arthritis of primary gout may be diagnosed by the clinical criteria listed in Table 2. If six criteria are present, the probability of gouty arthritis (positive predictive value) is 88%. Conversely, if fewer than six criteria are present, the probability that a patient does not have gouty arthritis (negative predictive value) is 97%. Because the patients in this study were solicited from rheumatologists, the sensitivity and specificity of the criteria in other populations may be different.

The serum urate level is normal in 8% of patients with acute gouty arthritis, often because of drugs. Between 9% and 18% of patients with other types of arthritis have elevated serum urate levels.

Joint aspiration is helpful if the diagnosis is uncertain, such as during a first attack, or if septic arthritis is suspected. Fluid specimens should be sent for Gram's stain, culture and examination for crystals. Urate crystals are needlelike and negatively birefringent. Under a red filter, they appear yellow when parallel to the axis of the polarizing filter. In contrast, calcium pyrophosphate crystals seen in cases of pseudogout are blunter and are positively birefringent. False-negative results from tests of joint aspirates occur in 5% of acute gouty attacks.

A therapeutic trial of colchicine is sometimes used as a diagnostic test for gout. Three quarters of patients with acute

gouty arthritis respond to colchicine and those with other forms of arthritis respond occasionally.

Treatment of Acute Gouty Arthritis

Nonsteroidal anti-inflammatory agents usually are effective treatment. Indomethacin is given at dosages of 50 mg every six hours for one or two days, then the dosage is tapered over the next several days. Common side effects are headache, nausea and abdominal discomfort. Dizziness, confusion, peptic ulcer disease, gastrointestinal bleeding and fluid retention also may occur.

Phenylbutazone is also effective, but because it causes more frequent gastrointestinal side effects and, rarely, bone marrow toxicity, many physicians are reluctant to use phenylbutazone for gout. The experience with other nonsteroidal agents is less extensive. Naproxen may be given as a 750-mg loading dose, followed by 250 mg three times a day. There is no conclusive evidence that any one nonsteroidal agent is superior.

Colchicine terminates most acute attacks. It is given by mouth 0.5 mg every hour until relief of pain or side effects occurs. Unfortunately, up to 50% to 80% of patients cannot tolerate colchicine given by mouth because of diarrhea, cramps or vomiting. Many clinicians prefer intravenous administration of colchicine, which avoids gastrointestinal side effects. The dose is 2 mg, which is diluted in 20 ml of saline before injecting into an intravenous line because sclerosis of the vein and extravasation may be painful. A dose of 1 mg may be repeated every 6 to 12 hours if needed. Because of possible bone marrow toxicity, no more than 4 to 5 mg should be given during a single gouty attack. A lower total dose should be given to patients receiving maintenance colchicine or who have liver or renal disease.

Intraarticular injections of steroids are useful in patients who cannot tolerate other drugs. Systemic steroids may be effective, but also may cause rebound attacks.

With many effective drugs available for acute gout, physicians should individualize treatment based on their own experience, the patient's clinical situation and the response of the patient in previous attacks. Both nonsteroidal anti-inflammatory agents and colchicine are more effective if given at the beginning of an attack.

Recurrent attacks of arthritis may be prevented by colchicine at a dosage of 0.5 mg once to three times a day. Recurrent attacks may also be an indication that giving drugs to a certain patient to lower the serum urate level would be helpful. These agents, however, should not be started during an acute attack because they can exacerbate or prolong it.

Tophi

Tophi have become increasingly rare since the widespread use of hypouricemic drugs. Common locations of tophi are the ear, hands, forearm, olecranon bursae and feet.

Renal Stones

Clinical Presentation

Between 10% and 25% of patients with gouty arthritis have renal stones. In 40% of patients, the stones precede arthritis. The risk of renal stones is 1 in 114 patients with gouty arthritis each year. Most stones are composed of uric acid (84%) and are radiolucent; some contain calcium oxalate or phosphate and are radiopaque.

In patients with gout, stones are more common when the concentration of urinary uric acid excretion is higher, occurring in 20% of patients excreting less than 700 mg each 24 hours compared with 35% in patients excreting between 700 and 1,100 mg and 50% in those excreting over 1,100 mg. However, 70% of patients with stones had a normal excretion of less than 700 mg.

The imperfect correlation between serum or urinary uric acid levels and stone formation may be partly explained by urinary pH. Uric acid is ionized and more soluble in alkaline urine; most stone-formers have relatively acidic urine. Because the pK_a of uric acid is 5.75, stones rarely occur if the urine pH is above 6.0. Other risk factors for uric acid stone formation are decreased fluid intake, dehydration, uricosuric drugs and ingestion of purine-rich foods.

Treatment of Stones

Increased fluid intake of more than 2 liters a day and alkalinization of urine to pH 6.0 often prevent further stones. In more severe cases, allopurinol dramatically reduces new stone formation. In addition, allopurinol may dissolve uric acid stones with prolonged administration.

Gouty Nephropathy

Clinical manifestations of gouty nephropathy are decreased concentrating ability, proteinuria or azotemia. Decreased renal function is uncommon, usually mild and often due to concurrent diabetes, hypertension or atherosclerosis. Although clinicians, to prevent azotemia, often administer drugs that lower the serum urate level, there is little evidence such treatment is effective.

Treatment to Lower Serum Urate Levels

When to start treatment to lower serum urate levels is controversial. Some experts recommend starting after one severe attack of arthritis or one renal stone. Many patients, however, prefer not to take daily medication, but instead to treat attacks when they occur. As in any chronic disease, patient understanding and compliance are essential. Taking hypouricemic drugs irregularly may precipitate gouty attacks.

Serum urate levels can be lowered either by a uricosuric agent that increases urinary excretion of uric acid, such as probenecid, or by allopurinol, which decreases production of uric acid. There are no good studies comparing these two approaches. For most patients uricosuric agents are preferred because life-threatening side effects with allopurinol, although rare, are being recognized more frequently.

Allopurinol should be used in patients with renal stones, tophi, renal failure and myeloproliferative diseases and in patients in whom therapy with uricosuric agents has failed and for those who cannot tolerate them. Allopurinol has also been recommended for the 10% to 20% of patients with primary gout who are "overproducers" and therefore overexcreters of uric acid. Overproducers excrete more than 800 mg per day of uric acid on an unrestricted diet or 600 mg per day on a purine-free diet. The rationale for using allopurinol in "overproducers" is that uricosuric agents, by further increasing uric acid excretion, might cause renal stones. The risk of

stones, however, may be overemphasized in patients who do not have previous renal stones, tophi or myeloproliferative diseases. A series reporting a 16% incidence of stones in those on probenecid therapeutic regimens included patients with tophi and previous stones. Physicians in this series did not follow the precaution of starting at low doses and increasing fluid intake. Moreover, in patients without tophi who are given uricosuric agents, the excess uric acid pool is excreted in a few days, after which urinary excretion (and presumably the risk of stones) returns to the original steady-state level.

Administration of uricosuric drugs should be started at low doses and fluid intake increased to prevent renal stones. *Probenecid* therapy is started at 250 mg twice a day, then increased to 500 mg twice a day three to four days later. Subsequently, the daily dose is increased by 500 mg every one to two weeks, to a maximum of 3 grams a day, until the serum urate level is normal. Usually 1 to 2 grams a day are needed. Side effects are gastrointestinal problems in about 8% of patients, skin rashes in about 5% and hypersensitivity reactions. Because probenecid inhibits renal tubular secretion not only of uric acid but also of a number of drugs, the serum concentration of penicillin, cephalosporins, indomethacin and methotrexate is increased.

Treatment with sulfinpyrazone is started at 50 mg twice a day and gradually increased in a similar manner as probenecid therapy. Usually 300 to 400 mg is needed, given in three or four divided doses. Gastrointestinal toxicity is more frequent than with probenecid. Skin rashes and bone marrow suppression may also occur.

In 25% of all patients receiving uricosuric agents normal serum urate levels are not achieved, usually because of azotemia or the concomitant use of low doses of aspirin.

Allopurinol in a single daily dose of 300 mg usually lowers serum urate levels to normal. A few patients require larger doses. Gastrointestinal intolerance has been reported in 0.4% to 16% of patients and skin rashes in 1.8% to 10%. Life-threatening hypersensitivity reactions involving skin, liver and kidney were reported in 2 of 1,835 patients; such reactions are fatal in 26% of cases. Adverse effects are more common in patients with renal failure or those taking thiazides, ampicillin or amoxicillin. Allopurinol may potentiate the therapeutic effect of sodium warfarin, azathioprine and 6-mercaptopurine.

Whenever either a uricosuric agent or allopurinol is given, colchicine, 0.5 mg twice a day, should also be administered to prevent gouty attacks. Therapy with colchicine should be continued until the serum urate concentration has been normal for 6 to 12 months. Limiting intake of alcohol and purine-rich foods and losing weight may reduce symptoms, but rapid weight loss should be avoided because ketosis may precipitate gouty attacks.

A common problem is a patient with recurrent gouty arthritis who takes a diuretic drug. Reasonable approaches are to discontinue giving the diuretic if possible—that is, by using a β-blocker alone for hypertension—to substitute spironolactone or triamterene, which do not increase serum urate, or to add a uricosuric agent.

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Medical Thermometry—A Short History

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The instrument trains . . . it exacts accuracy and teaches care; it creates a wholesome appetite for precision, which, at last, becomes habitual.

SILAS WEIR MITCHELL, 1891

In their attempt to pinpoint the exact nature of disease, doctors throughout the ages have looked for idiopathic signs from which they might learn. Among those signs, fever has always held a central place.

Before the invention of the thermometer, physicians used three principal methods for ascertaining temperature: the patient's appearance, the patient's own perception of body heat and the use of the "educated hand" to determine the febrile state of the body. Of these methods the physician's hand remained the standard medical means for estimating temperature. In hand thermometry, doctors were taught to use several fingers or the whole hand, depending on the surface to be examined. The hand was not simply placed on the skin surface but

> remain[ed] hovering a while above or near, to perceive the heat exhaled therefrom; then enter[ed] upon a slight contact with this surface to receive the impression of its most superficial temperature; then by a firmer pressure receive[d] the full impression of the skin's temperature; then by gradually deeper pressures acquire[d] the impressions of the deeper seated combustions.

Each of these pressures with their varying impressions of heat was assessed separately in the artful science of medicine.[1(p255)]

Early History

Since the early Greeks, if not before, physicians identified preternatural heat as a disease entity in itself; only later did heat become a pathognomonic symptom of disease. Hippocrates had noted temperature as it affected different parts of the body and had insisted that physicians recognize its signs and use agents to elevate the temperature when depressed and lower it when raised. Subsequent physicians had also noticed its effect on the body in disease. Galen (131-201 AD), the founder of experimental physiology, described fever as preternatural heat, or *calor praeternaturam.* Few found fault with this description although some preferred to use terms such as "hot skin," "tissue change," "quick pulse," "turbid urine" and "continuous fever" to further delineate fever as heat. Although heat and cold played a significant role in the humoral theory of disease, ironically, aside from the simple recognition of the two separate states, little effort was made to measure either.[2,3]

Within a decade of the astronomer Galileo's invention of the open thermometer or thermoscope sometime between 1593 and 1597, efforts were undertaken to develop an instrument that measured the difference between normal and abnormal temperatures in the human body. Sanctorius of Justipolitanus (1561-1636), a forerunner of the iatromechanical school and professor of medicine at Padua from 1611 to 1624, took a keen interest in air and body temperatures and as early as 1612 had constructed a crude thermometer for use in disease. Patients either grasped the bulb of the thermometer and breathed into a hood or took the bulb by mouth. In his *Ars de Statica Medicina* (1614) and later in his *Commentaria in primam fen primi libri Canonis Avicennae* (1625), Sanctorius noted that both body heat and body weight affected the constitution.[4,5] Besides a thermometric instrument that measured the variations in temperature of the human body, Sanctorius also devised several medical instruments, including a pulsilogium, or pulse-clock, and a trocar.[6(p24)]

Following the invention of the mercury thermometer by Gabriel Fahrenheit in 1714, Hermann Boerhaave (1668-1738) and his pupils Gerhard van Swieten (1700-1772) and Anton de Haen (1704-1776) noted the instrument's potential usefulness in medicine. The thermometric scale of Anders Celsius, commonly known as the centigrade scale (1742), was in general use in France and Germany, whereas the Fahrenheit scale (1714) remained popular in England and the United States for both meteorologic and medical purposes. A third scale, developed by Reaumur, was used over large portions of eastern and southeastern Europe. While Boerhaave gave only passing reference to the thermometer, van Swieten, professor of medicine at the University of Vienna, recommended that fever should be measured with a thermometer rather than perceived by hand. Van Swieten recommended the mercurial thermometer and applied it to both the mouth and axilla following the technique used by Fahrenheit. In his *Commentaries Upon the Aphorisms of Dr Hermann Boerhaave* (1744), van Swieten remarked:

> When such a thermometer, first used on a healthy man, and marked accordingly on the scale, is either held in the hand of a fever patient, or the bulb placed in his mouth, or laid on his bare chest, or in his axillae . . . the ascent

(Haller JS Jr: Medical thermometry—A short history [History of Medicine]. West J Med 1985 Jan; 142:108-116)

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of the mercury to different elevations will show how far the fever heat exceeds the natural and healthy.[7(p26)]

Anton de Haen, a clinical teacher of medicine at the Vienna Hospital, was fully convinced of the thermometer's usefulness and drilled students in the importance of body temperature in fever disorders. He made his point at bedsides, teaching that the only safe way to determine fever lay in the use of the thermometer. No longer would a physician's touch or the patient's perception be adequate, especially when the shivering patient complained of extreme coolness while, in fact, registering a temperature three or four degrees above normal. De Haen's thermometric studies, scattered through the 15 volumes of his *Ratio Medendi* (1757-1773), noted the temperature of healthy as well as diseased persons, the increase in temperature in the aged, diurnal fluctuations, the discrepancies between pulse and temperature in certain diseases, the differences between actual temperature and a patient's perception, the changes in temperature as a sign of convalescence and the relation of heat and the action of certain drugs.[8] De Haen's observations were buried in his immense treatise, and little noted.

Several 18th-century English contemporaries of de Haen, most notably Sir Charles Blagden (1748-1820), John Fordyce, Sir Joseph Banks and Solander, carried out experiments on animal temperatures that were subsequently published in 1775 in *Philosophical Transactions*. Placing themselves in heated chambers, they were able to establish that animal heat is independent of external temperature.[9,10] Also exemplary of the early fascination with the distinction between animal heat and external temperature was Governor Henry Ellis of Georgia, a naturalist who noted that "a thermometer standing at the end of my nose would often stand at 105 degrees, while in close contact with my body I would never get it above 98 degrees."[2(p433)] Then, too, Ben Franklin had observed about 1750 that although the outside temperature was 100°F, his own body remained at 96°F, proving to his satisfaction that warm-blooded animals had the ability to maintain a fixed temperature regardless of the climate or season.[11,12]

The most accurate 18th-century observations of healthy people and animals were found in the published works of George Martine (1702-1741), a graduate of Edinburgh and Leiden and a member of the mechanical school, who theorized that animal heat resulted from the velocity of the blood moving through the vessels.[13,14] His *Essays Medical and Philosophical* (1740)[13] spurred the subsequent work of Macard in 1741[15] and the experiments of Georg Pickel (1751-1838) in 1778.[16] Observations by George Cleghorn (1716-1789) in 1768[17] and John Lining (1708-1760) in 1748[18]on temperature among victims of malarial fever, of Charles Blagden in 1775,[12] of John Hunter (1728-1793) in 1793[19] and of James Currie in 1797 indicated a steady, albeit limited, interest in the temperature of healthy persons and the changes brought on by disease.

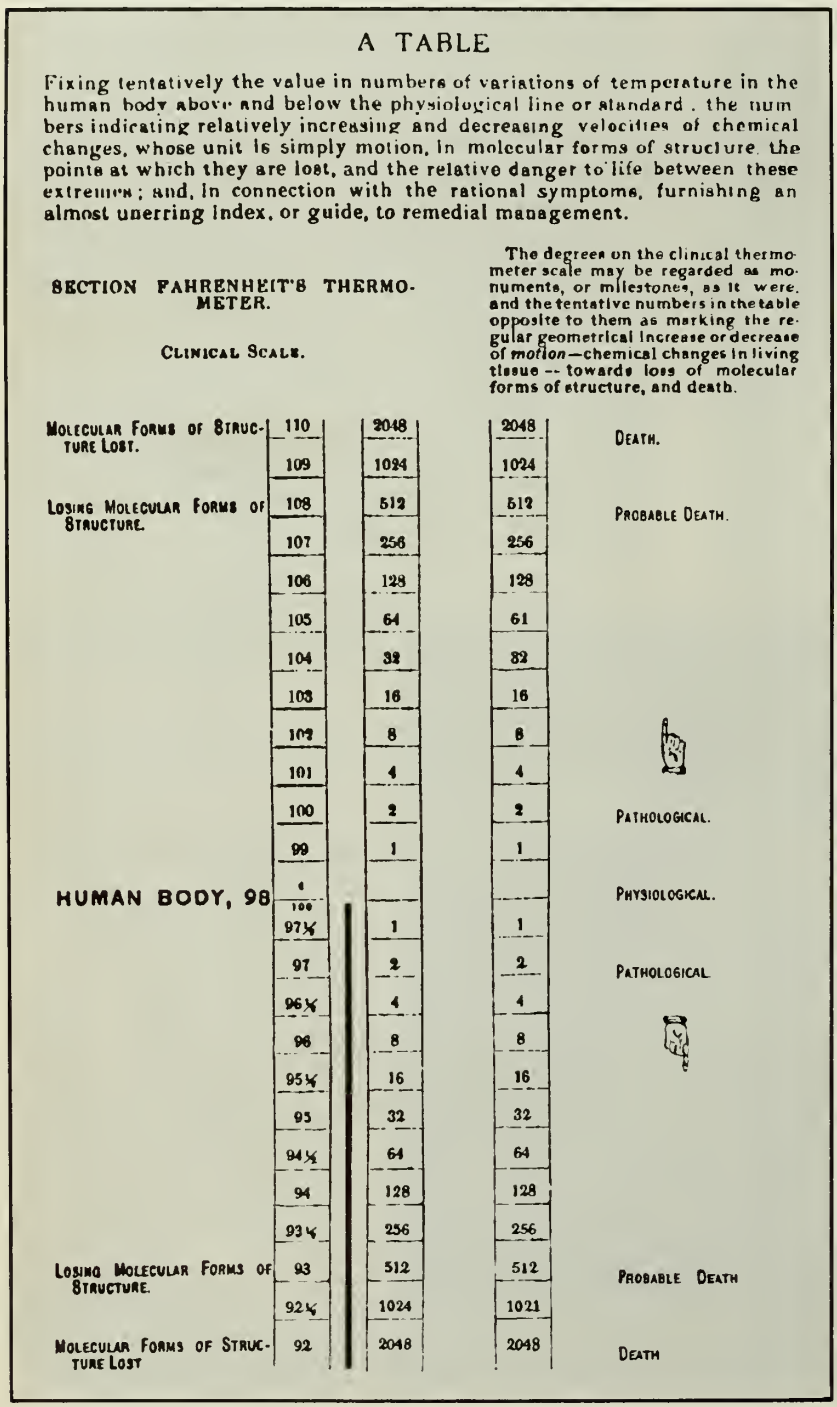
John Hunter in his *Observations on Certain Parts of the Animal Economy* (1792)[20] believed that heat arose from "a principle so connected with life that it can and does act independently of circulation, sensation and volition, and is that power which preserves and regulates the internal machine." The surgeon and physiologist added to existing data on temperature when he argued against Martine's theory that temperature was produced by the blood's circulation. "It is very evident," Hunter countered, "that warmth depends on a different principle, which is intimately connected with life itself, and is a power which maintains and regulates the machine, independent alike of the circulation, the will, and of sensation."[19(p338)]

La Température.
— Beau fixe!... Oh! oh! mais, je lui ai mis un baromètre!!!

Figure 1.—Lithography by Jules Abel Faivre (1867-1945) depicting use of a barometer (courtesy of the National Library of Medicine, Bethesda, Md).

Concurrent with the speculations of physicians were the chemical explanations of Antoine-Laurent Lavoisier and Pierre-Simon Laplace who in 1780 attributed animal heat to the combustion of oxygen with hydrogen and carbon during respiration.[21] Their views, however, were not received warmly by the medical profession. Sir Benjamin Brodie (1783-1862) of St George's Hospital, for example, reported in 1812 that, as a result of experiments carried out on the spinal column of animals, he had determined the source of animal heat to be the nervous system.[22,23] Brodie's theory and the earlier observation by de Haen on the brief rise in temperature after death caused the views of Lavoisier and Laplace to remain outside the mainstream of medical thinking until the later works of George von Liebig (1827-1903), Jules Robert von Mayer (1814-1878), Hermann von Helmholtz (1821-1894) and James P. Joule (1818-1889) finally carried the day.[24-27] Only after the experiments of Rudolph Virchow (1821-1902) and Claude Bernard (1813-1878) was the role of the nervous system in the production of fever defined.[28,29]

In the meantime, James Currie (1756-1805) built on the earlier observations of Martine by testing the effects of warm and cold baths, digitalis, opium, alcohol and diet on body temperature in typhoid fever. Known as the father of hydrotherapy, he advocated cold effusions in treating fevers but cautioned that they be used only when the heat of the body was elevated considerably above the natural body temperature.



A TABLE

Fixing tentatively the value in numbers of variations of temperature in the human body above and below the physiological line or standard, the numbers indicating relatively increasing and decreasing velocities of chemical changes, whose unit is simply motion, in molecular forms of structure, the points at which they are lost, and the relative danger to life between these extremes; and, in connection with the rational symptoms, furnishing an almost unerring index, or guide, to remedial management.

SECTION FAHRENHEIT'S THERMOMETER.

CLINICAL SCALE.

The degrees on the clinical thermometer scale may be regarded as monuments, or milestones, as it were, and the tentative numbers in the table opposite to them as marking the regular geometrical increase or decrease of *motion*—chemical changes in living tissue -- towards loss of molecular forms of structure, and death.

MOLECULAR FORMS OF STRUCTURE LOST.	110	2048	2048	DEATH.
	109	1024	1024	
LOSING MOLECULAR FORMS OF STRUCTURE.	108	512	512	PROBABLE DEATH.
	107	256	256	
	106	128	128	
	105	64	61	
	104	32	32	
	103	16	16	
	102	8	8	
	101	4	4	
	100	2	2	PATHOLOGICAL.
	99	1	1	
HUMAN BODY, 98	98			PHYSIOLOGICAL.
	97½	1	1	
	97	2	2	PATHOLOGICAL.
	96½	4	4	
	96	8	8	
	95½	16	16	
	95	32	32	
	94½	64	64	
	94	128	128	
	93½	256	256	
LOSING MOLECULAR FORMS OF STRUCTURE.	93	512	512	PROBABLE DEATH
	92½	1024	1021	
MOLECULAR FORMS OF STRUCTURE LOST	92	2048	2048	DEATH

Figure 2.—An 1872 table of the Fahrenheit scale (from McElroy[43]; courtesy of California State University, Long Beach).

"In taking the heat of the patient," Currie wrote, "I have generally used a small mercurial thermometer of great sensibility, with movable scales . . . and I have introduced the bulb under the tongue, with the lips closed, or under the axilla, indifferently. . . ."[30(pp35-36)-32]

The early years of clinical thermometry suffered from the lack of accurate instruments (Figure 1). Temperatures as high as 118°F were recorded in the 19th century—records that were not especially rare. According to one physician, a patient who had fallen from a horse registered a temperature of 110°F for several consecutive days, attaining on one occasion 122°F![33] However, the availability of more accurate instruments led to the work of Antoine Cesar Becquerel and Gilbert Breschet who, in 1835, established the mean temperature of a healthy adult at 37°C or 98.6°F.[1(p2),34]

By 1840 investigations had begun in earnest on the temperature of the body in both health and disease. No longer were experiments viewed in isolation; indeed, they became clinically important. Thermometric observations were prominently recorded in medical articles and comparisons were made with temperatures taken at various periods of the day and with previous variations noted in the same disease among other persons. Exemplary of these efforts were the investigations of Gabriel Andral (1797-1876),[35,36] August Gierse,[37] Edward Hallman (1813-1855),[38] Henri Roger (1809-1891)[39] and Jean-Nicolas Demarquay (1814-1875).[12,40]

Although thermometric investigations had provided a wealth of information on temperature in health and disease, there were as yet no laws derived from those studies that clearly justified to general practitioners the practical application of the thermometer. To be sure, the elevation of temperature had been noted in disease but formulations of any fixed rules regarding specific diseases were still to come. What prevented these early observations from becoming guiding medical principles were the still-little-understood laws of heat and the realization that the human body was at one in its movements with the forces outside it. These impediments were put aside in 1842 to 1845 when surgeon Robert Mayer laid down the essential work for the unity and correlation of forces in physiologic processes. Mayer's findings were followed by the investigations of Hermann von Helmholtz, James P. Joule of Manchester and Gustave A. Hirn (1815-1890) of Colmar, whose theories of heat production made body temperature as a convertible force subject to set laws more understandable. Following their efforts, physicians found it easier to translate the findings of the thermometer to both physiologic and pathologic processes.[41(p8),42]

By the mid-1860s, use of the clinical thermometer had led to certain conclusions. For one thing, doctors recognized the importance of body temperature and the physiologic significance of its variations (Figure 2). Body heat was admitted to result from chemical transformations occurring in the normal waste and repair of the body tissues; the temperature produced by this action was recognized as uniform—rarely varying from one person to another. In *Physiological Researches,* published in 1863, John Davy (1790-1868) had determined that variations occurred as a result of exercise, the ingestion of food or drink, external temperature and from the greater activity of the bodily processes in infants and children.[44,45] By the 1860s, too, physicians had concluded that the temperature was a better clinical guide than the pulse because it was not easily affected by nervous debility or excitement.[46,47]

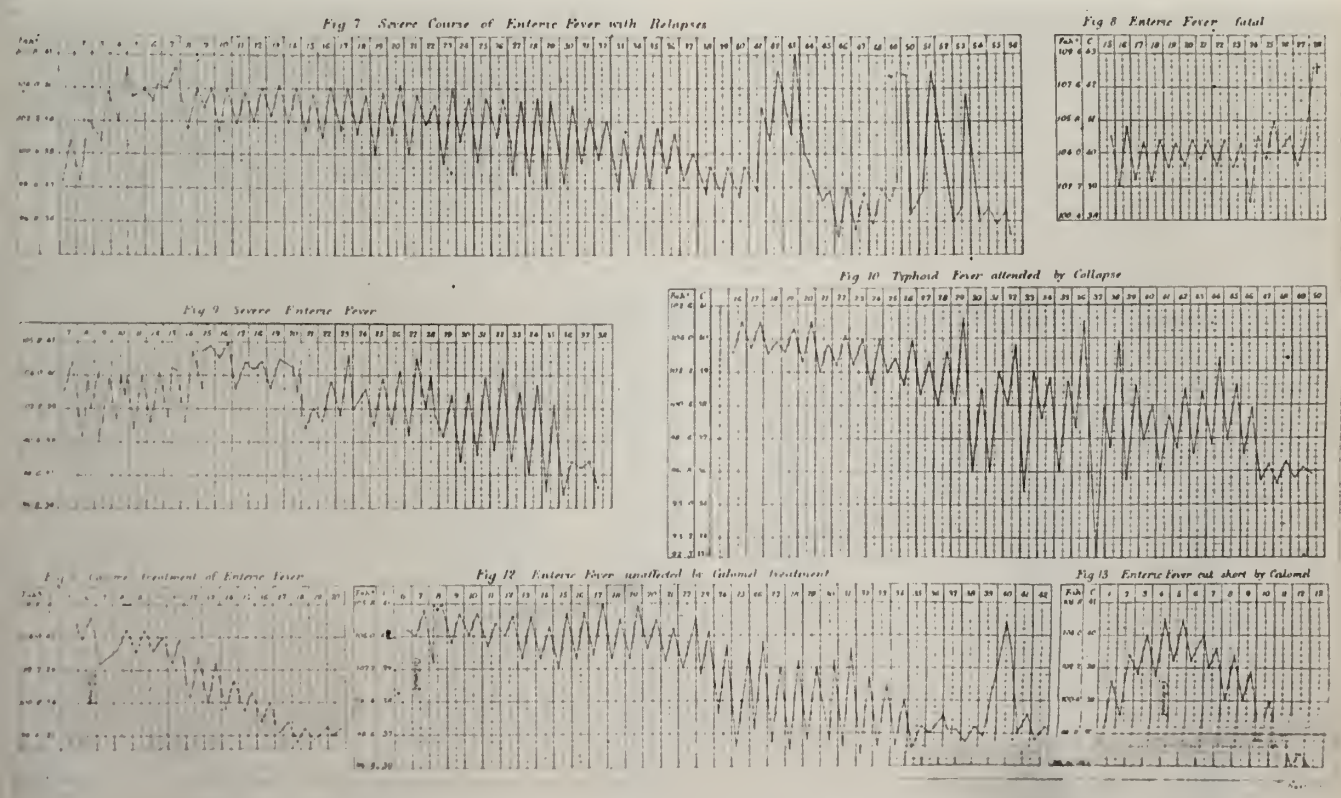


Fig 7 Severe Course of Enteric Fever with Relapses
Fig 8 Enteric Fever fatal
Fig 9 Severe Enteric Fever
Fig 10 Typhoid Fever attended by Collapse
Fig 12 Enteric Fever unaffected by Calomel treatment
Fig 13 Enteric Fever cut short by Calomel

Figure 3.—Temperature charts (from Wunderlich[41]; courtesy of California State University, Long Beach).

Carl Wunderlich

By the second half of the 19th century, noted physicians and surgeons had begun to show more than casual interest in thermometry. Although significant studies had been published by Claude Bernard in France, by John Davy, Daniel Blair[48] and Sidney Ringer (1835-1910) in England[49] and by Barensprung[50] and Ludwig Traube (1818-1876) in Germany,[51] the first truly classical study of the thermometer in clinical practice came with the publication in 1868 of Wunderlich's *Das Verhalten der Eigenwärme in Krankheiten*. The first English edition of this work was published in 1871.[41] Carl Reinhold Wunderlich (1815-1877) of Wurttemberg had first introduced the use of the thermometer in his clinic in 1851 at the recommendation of Traube, whose work on the antipyretic effects of digitalis on body temperature Wunderlich found beneficial. Over a period of 15 years and with an increased appreciation for the value of the thermometer in clinical medicine, Wunderlich noted that there were "no patients in my hospital wards whose temperature has not been taken; and, although at first this was only done twice a day, for the last ten years from four to six daily observations have been made in cases of fever, and in special cases even more frequently."[41(pp38-39)] After obtaining nearly 100,000 observations, Wunderlich discerned certain traits which, when charted, showed that disease obeyed fixed laws that could be shown by the course of the temperature (Figure 3). In all, Wunderlich estimated having taken several million observations of some 25,000 specific cases.

The care with which Wunderlich had accumulated his statistics and the careful tabulation of his results convinced the medical profession of the importance of accurate knowledge of temperature in clinical diagnosis, prognosis and the treatment of disease. Wunderlich made the decisive determination for pathology—that there was constancy of temperature in a healthy person and variation of temperature in disease. What followed from these two ascertainable facts were some 40 principles that he derived from his experiments and observations.[41(pp1-18)]

From his studies Wunderlich was able to trace the natural history of specific diseases and establish the unquestioned foundation of thermometric change and the distinguishing features of typhoid fever. Soon, observations of temperature during pregnancy, delivery and the postpartum period and in various internal diseases became widely acknowledged. And after Theodor Billroth's proofs in 1868 of the importance of temperature in the diagnosis of surgical diseases, the thermometer was seldom out of sight of surgeons.[52,53] "A physician who carried on his profession without employing the thermometer," concluded Wunderlich, "was like a blind man endeavouring to distinguish colours by feeling."[54(p451)]

Medical Response to Clinical Thermometry

Wunderlich's findings received enthusiastic support throughout Europe and America. Indeed, many of the early studies that had taken place were not justified in the light of the principles laid down by Wunderlich and his followers. From Jean-Martin Charcot (1825-1893)[55] and Sigismond Jaccund (1830-1913) in France,[56] to Sidney Ringer and William Aitken in England,[57,58] to John C. Draper (1835-1885),[59,60] Bennet Dowler (1797-1879)[61] and Edward Seguin in America, medical thermometry assumed an intelligent application that firmly established its practical value in medicine. Use of the thermometer facilitated the clinical recognition of disease, aided practitioners in arriving at certain and safe conclusions regarding the nature of disease, allowed physicians to understand the natural history of diseases in which fever was present and provided an accurate means for monitoring various therapeutic regimens.

The earliest thermometers used in the British Isles were imported from Leipzig by Griffin. The first instruments manufactured in England were those of instrument maker Louis P. Casella, under the direction of William Aitken of the Royal Victoria Hospital. For general practice, however, the curved nonregistering thermometer by Casella was considered too cumbersome (Figure 4). As one physician at Guy's Hospital recalled, "I think it was nearly a foot long and was so great a novelty that it was taken to a southeastern meeting of the

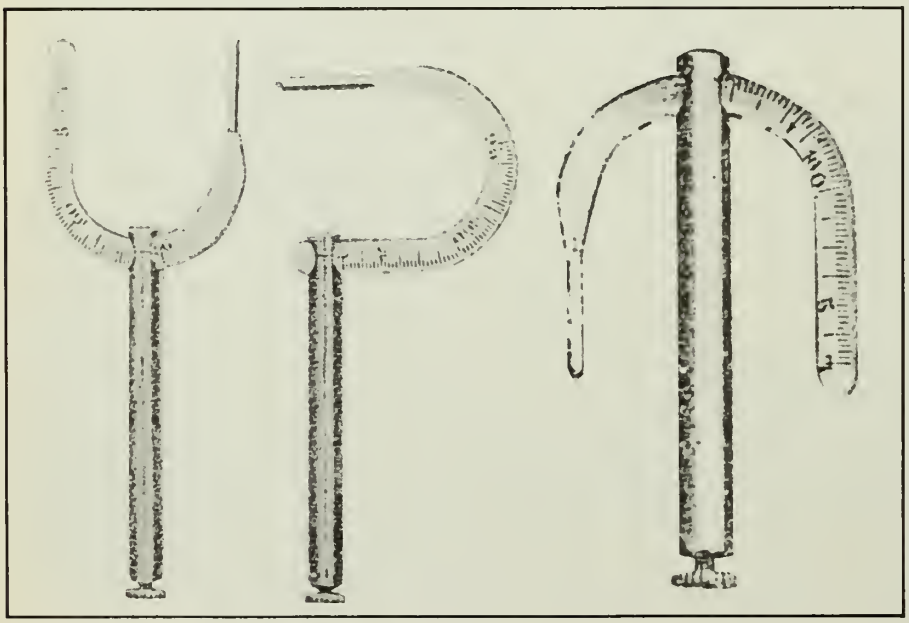


Figure 4.—Curved thermometers designed for insertion under patient's tongue; made for T. Wilson Parry by Francis Cooper of Tottenham Lane, Hornsey (from Br Med J 1912; 1:1137; courtesy of California State University, Long Beach).

British Medical Association for exhibition, where the members regarded it with much curiosity and interest, although, I am sorry to say, one or two with ridicule."[11]

Having recognized the need for a more portable instrument, T. Clifford Allbutt asked Casella to make a pocket thermometer. When Casella showed no interest in the undertaking, Allbutt then worked with Harvey and Reynolds of Leeds to manufacture an accurate thermometer that could be carried in a safe and portable case. With the size of the instrument reduced, clinical thermometry became a regular part of medical practice and firms such as Harvey and Reynolds and Hawksley of London supplied registering thermometers that were easily portable.[2(p437),62]

The special laws of thermopathology required that thermometers be designed specifically for physicians and correlated with the variations in physiologic functions. This in turn implied a need for thermometers that were adaptable to the body cavities—whether the axilla or groin, mouth, rectum, urethra, vagina or hand. By the 1860s, the axilla had become the most universally adopted, convenient and reliable point of application. Recognition of the mouth as a source of disease transmittal acted as a restraint on its use for thermometic measurement. "I have seen the thermometer used when the amount of mucus accumulated on it was so great as to make it almost difficult to see the register," commented one physician in 1891.[63] He noted that most practitioners simply wiped the instrument with a handkerchief, towel or even bedclothing, thereby preserving the germs "to be conveyed to the next unfortunate, who may be the first patient called upon." Not until doctors recognized the importance of alcohol, bichloride of mercury, hydrogen peroxide, potassium permanganate and other germicidal agents in the late 1890s did oral thermometry begin to replace the axilla as the most popular point of application.[63-65]

One of the early problems the manufacturers of clinical thermometers faced was that of glass shrinkage, which distorted the thermometer's accuracy.[66] To avoid this, thermometers were "seasoned" or stored for two or three years before being put into use; any subsequent calibration was generally good for the life of the instrument. English physicians who wanted greater precision in thermometric measurement could purchase seasoned thermometers certified by the observatory at Kew Gardens, London. The certificate provided a scale of readings corrected with standardized instruments. For obvious reasons, the certificate proved highly marketable for manufacturers; but the demand worldwide for accurate thermometers tempted less scrupulous manufacturers to sell certified—but unseasoned—instruments that lost most of their utility within a year. In 1880 the Winchester Observatory at Yale College established a thermometric bureau under the management of Dr Leonard Waldo to serve the needs of the American market. Within a short time the observatory at Harvard University offered a similar service.[67,68]

As doctors became more sophisticated in using the thermometer, they divided diseases into distinct periods reflective of thermometric change. The first period, known as the initial, effervescent or pyrogenetic stage, marked the gradual increment of body heat; the second stage of full febrile development was known as the fastigium. The third or final period, known as defervescence, marked the decline of the temperature to normal. When viewed on a thermometric chart, the entire course of a disease—from pyrogenesis to defervescence—was brought into view. Especially during prolonged illnesses in which changes were gradual rather than sudden, the chart became an important guide to diagnosis and prognosis. In its entirety, the chart was a visual record of the history of a given disease (see Figure 3).[69,70]

American Thermometry

According to Edward Seguin, an avowed disciple of Wunderlich, America could claim Josiah S. Lombard,[71] Lucius D. Bulkley,[72] H. C. Daguin, Bennet Dowler, Abraham Jacobi (1830-1919),[73] Austin Flint (1812-1886),[74] Joseph Jones (1833-1896)[75] and Jacob DeCosta (1833-1900)[76] as men who aided measurably in the understanding of medical thermometry.[1(p9)] Except for the work of Dr Jones of Georgia, however, whose experiments were published in the *Transactions* of the American Medical Association in 1859, clinical thermometry had few American adherents before the mid-1860s.[77,78] During the Civil War, John Shaw Billings recalled having used a thermometer when caring for the wounded in Richmond in 1862, and in 1866 the *Army Medical Department Reports* included the earliest series of temperature charts published by a medical officer in the public services.[12,79]

American hospital thermometry was introduced in the mid-1860s in the New York Hospital and later in the Bellevue Hospital. In 1866 Seguin and William H. Draper carried out tests in the New York Hospital on the application of thermometry in disease. Both recognized disease as "a disorder of the mathematics of life" and were anxious to transform thermometry into thermography by way of "medical mathematism."[1(pp309,384)] Of interest to Seguin and Draper were the distinctions that the use of the thermometer allowed them to make between typhus, typhoid and remittent and intermittent fevers. Draper prepared his own chart of the vital signs, which he attached to the beds of his patients in the New York Hospital; Austin Flint borrowed a similar chart developed by Jacob DeCosta, which Flint introduced at Bellevue.[80,81]

Although hospital physicians and their staffs laid the foundations of medical thermometry in America, it quickly spread into the hands of family practitioners and from there to nurses and the family circle. By the 1870s, Seguin was encouraging the development of "family thermometry."[82] His espoused purpose was to encourage family practitioners to gain "intelligent cooperation of women in the mechanical part of positive diagnosis" and also to rescue women "from the clutches of quackery and of medical theurgism." Mothers who could read thermometers could render invaluable service to their families in times of illness, provide important information for physicians and serve notice to quacks and assorted mediums that their suspect therapeutics were no longer accepted in the home circle. Thermometry, Seguin concluded, "is not only knowledge, but social power."[83]

At the height of the discussion in America on the implications of medical thermometry, Ohio physician Z.C. McElroy, a follower of the materialistic interpretation of Ernst Haeckel and Thomas H. Huxley, placed the thermometer's use within a broader philosophic framework.[43] McElroy praised the thermometer as an instrument of precision but argued that only when understood in its relationship to the totality of organic life could the thermometer be given its appropriate significance in the diagnosis, prognosis and

treatment of disease. Philosophy with its broader vision confirmed that the thermal state of the body was due to changes of matter and that "in organic life temperature is wholly due to retrograde chemical metamorphosis, and, with almost certainty, to the retrograde metamorphosis of solid tissue." Physiology encompassed an understanding of definite molecular forms of structure, each capable of specific functions and each with its own specific rate of waste and repair. Pathology, on the other hand, consisted of variations in the "physiological velocities of repair and waste" above or below the standard; and, finally, therapeutics consisted of remedial agencies designed "to promote, retard, or change the velocity of the chemical changes of matter in either or both the interest of repair or waste." The purpose of the clinical thermometer was to measure the physiologic or pathologic velocity of chemical change occurring in the human body and express that change in the form of a number.[43]

Medical therapeutics, insofar as it approached being an exact science, explained McElroy, made use of remedial agencies for their sole ability to influence motion—"chemical changes of matter, ascending to or descending from molecular forms of structure of living beings."[43] The thermometer permitted physicians to evaluate the condition of molecular change in the body as a means of diagnosing a pathologic state, of making an accurate prognosis of the pathologic state and in guiding therapeutic measures designed to correct the condition of molecular motion in the body.

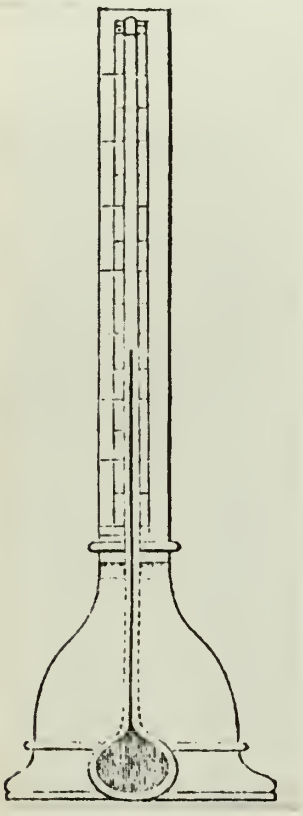


Figure 5.—A surface thermometer used for examination of tumors and diseased joints (from Spurgin[84]; courtesy of California State University, Long Beach).

Surface Thermometry

Not all medical thermometry was limited to the measurement of the body's internal temperature. Recognizing variations of temperature in different parts of the body and believing that those surface variations would be helpful in diagnosing disease, J. Spurgin, MD, constructed in 1857 a "thermoscope," consisting of a common thermometer whose glass bulb was suspended in a hollow cone of wood, the glass shaft rising out of the cone and fixed to a graduated ivory index (Figure 5).[84] By comparing surface temperatures, Spurgin was able to treat breast tumors, having discerned that the heat of the tumor was several degrees higher than surrounding tissue. Satisfied with the results of the instrument, he recommended the thermoscope in the diagnosis and treatment of tumors and diseased joints.

A few years later, Pierre Paul Broca's (1824-1880) interest in the cephalic index was expanded to "cerebral thermometry."[85] Using a graduated thermometer (Figure 6), Broca found it possible to obtain the mean temperature of the brain, of the right hemisphere compared with the left and of the frontal, temporal and occipital lobes. On the basis of observations on interns and students in his wards at the Hôpital des Cliniques, Broca concluded that the temperature was higher on the left side of the brain at repose, but when at

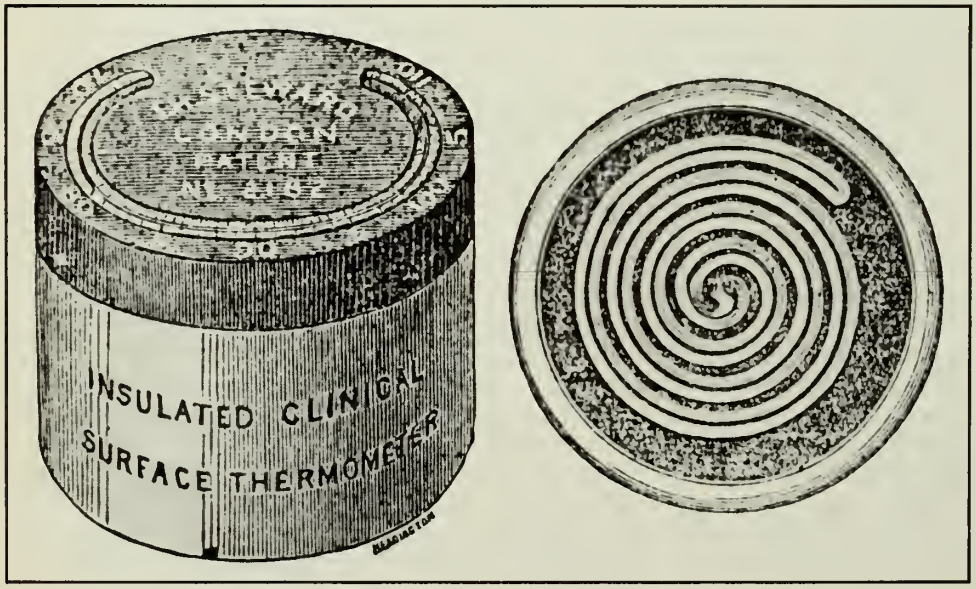


Figure 6.—A surface thermometer for cranial thermometry. **Left,** Steward's surface thermometer, side view. **Right,** View of undersurface, representing flatly coiled tube containing mercury. (From Hart[85]; courtesy of California State University, Long Beach.)

work, equilibrium was established. Although he began his investigations in 1869, Broca did not apply his research to the diagnosis of cerebral afflictions until 1873 when cerebral thermometry became a means of determining the existence of a cerebral embolism.[85]

Soon after notice of Broca's published work appeared in 1877, Landon Carter Gray, MD, of Brooklyn repeated the experiments of Broca on physicians and medical students at the Long Island College Hospital.[86] His conclusions, which were remarkably similar to those of Broca, enabled him to diagnose the existence of an intracranial tumor, afterward verified by postmortem examination.

Conclusion

In his address before the Congress of American Physicians and Surgeons in 1891, Silas Weir Mitchell noted that medical instrumentation forced physicians "to learn, to be rapid, and at the same time [to be] accurate." As in factories where machines were lifting a generation of workers to the "general level of acuteness of observation," the use of diagnostic instrumentation had lifted the medical intellect beyond all previous boundaries.[87(p164)] From Hippocrates who first recognized the importance of temperature as a sign of acute disease, to Sanctorius who first applied the thermometer to the human body, medicine had made a significant departure from art to science. And, again, with de Haen who demonstrated the practical application of thermometry in clinics, Becquerel who discovered the norm in mathematical diagnosis and Wunderlich who demonstrated the rules of ustion in disease, medicine could look back on a progression of events that ultimately placed clinical thermometry among the more significant achievements in medical science.

Although recognizing the ability of precision instruments to heighten levels of knowledge and provide an additional aid to diagnosis, Mitchell warned of the potential risks that instruments could bring "to the lazy or the unthoughtful." Physicians could become so dependent on instruments as to lose the power or even the desire to reason on the complex phenomenon of disease. Unless doctors "keep ahead of their instrumental aids," he remarked, they "will merely dementalize them, and but measurably lift the mass without in proportion advantaging the masters of our art, who were so easily masters in days when the erudite touch was more uniquely advantageous than it is today."[87(p165)] As Mitchell so rightly understood, true medical science resided not in the instrument, however precise, but in the intellect.

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Treatment of Herpes Zoster With Corticosteroids—Fact or Faith?

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It is a common practice to use systemic corticosteroids in managing patients with herpes zoster. The rationale for this is based on studies suggesting that the early use of systemic corticosteroids in herpes zoster significantly reduces the duration of an acute illness and the incidence of postherpetic neuralgia in patients older than 50 years.[1-3] To assess the use of this form of therapy, we surveyed a group of 73 practicing dermatologists* in January 1983 by means of a questionnaire. Of the 56 who responded, 46 (81%) routinely used corticosteroids in otherwise healthy patients older than 60 years who had early herpes zoster. An average of 68% routinely used corticosteroids in patients between 50 and 60 years of age. For patients younger than 50 years of age, only 20% (average) used corticosteroids routinely and this was more frequent in patients with cranial nerve involvement. Although the findings of this survey substantiate the common usage of corticosteroids in herpes zoster, a critical review of the literature indicates that the scientific basis for this practice is not as strong as one might think. We describe an approach for clinicians to use in assessing whether or not a therapeutic trial is valid and applicable in their own clinical settings, and then use this approach to appraise the major studies concerning systemic corticosteroids and herpes zoster.

In a guide published by epidemiologists at McMaster University, Canada,[4] to help clinicians read scientific articles critically, there are six simple criteria to distinguish useful from useless (and even harmful) forms of therapy. Briefly, these are the questions a reader should ask in judging a study about a form of therapy:

- *Was the assignment of patients to treatment groups really randomized?* It is well established that the most appropriate method for comparing different therapies is by means of a randomized control trial. Although randomization alone does not guarantee validity, a clinician should certainly turn to randomized trials in making therapeutic decisions if they are available in the literature. Case reports and studies with no control group can be put aside when randomized control trials exist.

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(Levinson W, Shaw JC: Treatment of herpes zoster with corticosteroids—Fact or faith? [Information]. West J Med 1985 Jan; 142:117-118)

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- *Were all clinically relevant outcomes reported?* In judging the value of a new drug, it is important that all outcomes including benefits and adverse side effects are noted. In addition, objective criteria for measuring those outcomes should be applied, and the investigator should be "blind" to the therapeutic group to which the patient was assigned, when measuring that outcome.
- *Were the study patients recognizably similar to your own?* Detailed description of the subjects is necessary to fulfill this criterion. A response to a particular therapy may be different, for example, in older versus younger patients, or in inpatients versus outpatients.
- *Were both statistical and clinical significance considered?* The importance of testing statistical significance is obvious since data can be deceiving. Statistical significance tells us the probability that the effect was real and not due to chance alone. Failure to test statistical significance should lead a reader to wonder why the author avoided the issue! Furthermore, not all data that are statistically significant will be of sufficient magnitude to have clinical impact. Readers must assess the clinical significance of results in light of their own clinical practice.
- *Is the therapeutic maneuver feasible in your practice?* Simply, the therapy should be described clearly so readers may judge whether they could actually use it in practice.
- *Were all patients who entered the study accounted for at its conclusion?* Again, bias may enter a study when not all patients are adequately followed up. For example, a subset of a study population may improve greatly with a new drug and hence not return for care. The group remaining in the study would overrepresent patients who did not respond as well to the treatment. This would lead readers to falsely conclude that the drug was less effective than it was in reality. The effect of inadequate follow-up on a study is unpredictable and may make a form of therapy look better or worse than it really is.

With these guides in mind, let us turn to evaluating the articles published about treatment of patients with herpes zoster with corticosteroids. There have been numerous reports suggesting the efficacy of steroids in preventing postherpetic neuralgia, but most of these have been either uncontrolled trials or case reports of a few patients.[5-7] There are two randomized control trials of systemic corticosteroids in herpes zoster. The first, by Eaglstein, Katz and Brown,[1] has been a major influence in dermatologists' practices since its publication in 1970. Keczkes and Basheer[2] provided a more recent study in 1980. Using the McMaster University criteria, we have critically reviewed each of these.

The trial by Eaglstein and co-workers was randomized and included a total of 34 patients—19 received a placebo and 15 received triamcinolone orally in a tapering three-week course starting with 48 mg a day for the first seven days. The average time between onset of lesions and the initiation of therapy was five days. The outcomes measured were healing time and presence of pain persisting two

months after the onset of skin lesions. Of 15 patients older than 60 years who were given a placebo, postherpetic neuralgia developed in 11 (73%), whereas only 3 of 10 of the triamcinolone group (30%) were affected. In none of the nine patients younger than 60 years did postherpetic neuralgia develop. Healing time was comparable in both groups.

This study did meet a number of the important criteria, but had several major shortcomings. First, there were too few patients younger than 60 years of age to draw any conclusions. It is therefore not clear whether the drug might have been helpful in this age group had a larger group of patients been tested. Although the incidence of postherpetic neuralgia is considerably less in younger patients,[8] corticosteroids could still have an important preventive role. Second, the study population included only patients with severely painful zoster admitted to an inpatient dermatologic service. As mentioned earlier, it is possible that responses to a particular therapy may be different depending on the population from which the study sample is selected. Patients with "severe" herpes zoster may respond differently to corticosteroids than do less severely affected outpatients. This does not negate the findings of this study but raises the question of the applicability of the treatment of routine cases of herpes zoster. Most important, this study did not report a statistical analysis of their data. We did a χ^2 analysis of the data and found their results insignificant at the conventional P value of .05. Hence, the possibility that these results occurred by chance alone is greater than what most clinicians and researchers would accept in making a therapeutic decision. This failure to reach statistical significance may have been due to the inadequate sample size (see below).

The other randomized trial by Keczkes and Basheer allocated 20 patients to each group and included only patients older than 50 years. One group received 40 mg of prednisolone orally for ten days with gradual reduction over the next three weeks, whereas the "control group" received carbamazepine, 100 mg, four times a day for four weeks. Postherpetic neuralgia occurred in 13 (65%) of the carbamazepine-treated group and in only 3 (15%) of the prednisolone-treated group. Skin healing was reported as significantly quicker in the prednisolone group (3.65 weeks) than in the carbamazepine group (5.25 weeks).

This study also has some major flaws. First, no true placebo group was studied. It has been suggested that carbamazepine alone is helpful in treating certain cases of postherpetic neuralgia.[9] Although this would tend to decrease the differences between the study groups, a true assessment of the response to prednisolone is not possible using this potentially active drug as the control. Second, this trial also included only patients admitted to hospital with "severe" herpes zoster. Third, the authors did not statistically analyze their data. We performed a χ^2 analysis of their data and found their results concerning postherpetic neuralgia significant at $P < .05$. Differences in healing time were also significant (Student's t test, $P < .01$). Finally, the clinician who followed the patients to evaluate the presence or absence of pain was not "blind" to the study group. We think the violation of this criterion is so important that we could not be confident of any results found in this study. It is imperative that the investigator does not know what drug the patient is receiving, particularly when the outcome measured is as subjective as pain.

What can be concluded about the role of systemic corticosteroids in herpes zoster? The case reports and the trials described above have all suggested that corticosteroids are effective in preventing postherpetic neuralgia and that there are no significant complications from this therapy. The results of the two trials reviewed, however, support this treatment only for severe disease. This of course does not rule out the possibility of benefit in less severe cases. Also, the fact that no cases of postherpetic neuralgia were found in the younger age groups does not rule out the possibility that corticosteroids would be beneficial in this population. Hence, despite the evidence suggesting benefit in older patients with severe disease, we conclude that an adequate randomized trial has not yet been done.

In our review, it is evident that several considerations in study design are necessary to answer the question. One is adequate sample size. A sample size larger than those used in the published trials to date is needed to achieve statistical and clinical significance.[10] Assuming a 70% occurrence rate of postherpetic neuralgia for patients older than 60 years, using conventional statistical limits (2-sided $\alpha = .05$, $\beta = .2$), a total sample size of at least 60 patients would be required to show a 50% reduction in postherpetic neuralgia in the treated group. Similarly, with a 25% occurrence rate as one might expect in patients younger than 50, a total sample size of approximately 300 would be required; a difficult task, but not impossible. In addition, true randomization must be used, a placebo control group must be incorporated and ideally outpatients should be studied. Finally, a double-blind design is essential since the outcome is subjective.

Is it necessary to design the perfect trial since the therapy itself has few complications and the suffering in postherpetic neuralgia may be great? In our opinion, the use of systemic corticosteroids may help prevent postherpetic neuralgia in all age groups. Unfortunately, at present the decision to use this treatment cannot be based on fact. We think that a properly designed trial could answer this therapeutic question conclusively and would be a significant contribution to the management of herpes zoster. We are investigating the feasibility of a multicenter trial.

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Neonatal Hyperviscosity Syndrome

PAUL Y. K. WU, MD
Los Angeles

THE HYPERVISCOSITY SYNDROME is a symptom complex associated with decreased blood fluidity, which is generally associated with an increase in erythrocyte mass. The mean cord blood hematocrit is 45±5% and 50 ±5% in preterm and term infants respectively if they are born at sea level. Values are somewhat higher in infants born in locations at higher altitudes. A central venous hematocrit of 65% or more is generally accepted as the definition of polycythemia.

Although polycythemia may be associated with hyperviscosity of the blood, the two conditions are not synonymous, as not all hyperviscous infants are polycythemic nor are all polycythemic neonates hyperviscous.

The viscosity of a fluid is defined as the ratio of shear stress to shear rate. Shearing occurs as the result of internal friction of the fluid layers moving over one another during flow. It can be measured with a cone plate viscometer (such as a Wells-Brookfield Micro-Viscometer) over a range of shear rates. Two commonly used shear rates for blood are 11 and 106 seconds^{-1}. These shear rates presumably approximate those in small venules and large arteries respectively. In several studies a direct curvilinear relationship has been found between hematocrit and blood viscosity, with viscosity increasing substantially at a hematocrit of more than 70%.

In contrast to Newtonian fluids, blood contains several factors that influence its viscosity:

- Cellular elements, erythrocytes, leukocytes and platelets. More recently the lack of erythrocyte deformability has been found to be an important factor.
- Plasma elements such as proteins, chylomicrons, electrolytes and water molecules.
- Velocity of flow.
- Suspension stability.

In addition, in narrower blood vessels the viscosity of blood depends more on the viscosity of plasma because the cells will gather in the faster axial zone, causing in effect a fall in hematocrit and blood viscosity (Fahraeus phenomenon). Because the plasma protein content is lower in neonates, this Fahraeus effect favors blood flow; however, sick neonates or infants of diabetic mothers may have macroproteins that can increase plasma viscosity.

(Wu PYK: Neonatal hyperviscosity syndrome [Information]. West J Med 1985 Jan; 142:119-120)

From the Newborn Service, Department of Pediatrics, LAC/USC Medical Center, Women's Hospital, Los Angeles.

Reprint requests to Paul Y. K. Wu, MD, Associate Director, Newborn Service, LAC/USC Medical Center, Women's Hospital, Room L-919, 1240 N Mission Road, Los Angeles, CA 90033.

Clinically the factors associated with increased incidence of hyperviscosity syndrome include

- Intrauterine hypoxia
- Intrauterine infection
- Developmental factors
  - Infants of diabetic or gestational diabetic mothers
  - Down's syndrome
  - Trisomy D
  - Adrenal hyperplasia
  - Oligohydramnios
- Placental dysfunction
  - Small for gestational age
  - Postmaturity
- Transfusion
  - Placental-cord
  - Twin-twin
  - Maternal-fetal
- Cyanotic congestion
  - Heart disease

Hyperviscosity may lead to sludging of blood flow with resultant impairment of tissue oxygenation and a tendency to form microthrombi. Impaired circulation and tissue hypoxia will result in the following disturbances: brain—central nervous system signs of irritability, jitteriness and convulsions, which may be associated with neurologic sequelae; heart—a fall in systemic cardiac output due to decreased venous return, an increased viscous load for the heart to pump and increased ratio of the right preejection period to right ventricular ejection time (RPEP/RVET); lungs—increased pulmonary vascular resistance leading to increased intrapulmonary shunting and poor gas exchange, producing symptoms such as cyanosis, tachypnea and cardiomegaly; kidneys—oliguria and hypoxic damage of glomeruli and tubules leading to proteinuria, hematuria, disturbances in sodium absorption and renal vein thrombosis; gastrointestinal tract—ischemia of bowel wall and necrotizing enterocolitis; blood—hypoxia, acidosis and hypoglycemia causing decreased erythrocyte deformability, thrombocytopenia, burr or fragmented cells and decreased blood flow, especially in the periphery; jaundice—probably due to breakdown of an increased number of damaged erythrocytes; hypoglycemia—nonnucleated erythrocytes have very little intracellular glycogen and therefore depend on serum glucose for their metabolism, and an increased number of erythrocytes may lead to greater glucose use. This may be an added etiologic factor in addition to tissue demands for glucose.

In addition to the underlying condition—such as small size for gestational age—the symptoms and signs associated with the condition include plethora, cyanosis, tachypnea, cardiomegaly, hypoglycemia, hypocalcemia, hypomagnesemia, hyperbilirubinemia, lethargy, poor feeding, jitteriness, seizures and oliguria.

Controversy exists as to when exchange transfusion, with either fresh frozen plasma or 5% salt-poor albumin solution, is warranted. This is largely because of

the inconsistent correlation between the presence of clinical symptoms and signs with polycythemia or in vitro measurements of blood viscosity. However, in view of the potential dangers of hyperviscosity and findings that document abatement of clinical symptoms and signs following exchange transfusion, it would appear reasonable to do a partial exchange transfusion when an infant's central hematocrit is greater than 70% or viscosity is greater than 22 centipoise at 37°C at a shear rate of 11 seconds^{-1}, or at lower central hematocrits (such as 63% to 70%) when they are associated with symptoms. The formula that can be used for calculating for an exchange transfusion is

$$\text{Volume of blood exchanged} = \frac{\text{blood volume} \times (\text{observed Hct} - \text{desired Hct})}{\text{observed Hct}}$$

where blood volume (neonatal) = 80 to 100 ml per kg of body weight and desired hematocrit (Hct) = 50% to 55%. Because fresh frozen plasma is a source of fibrinogen that can increase erythrocyte aggregation and thereby increase blood viscosity, 5% salt-poor albumin is the preferred solution used for partial exchanges.

Another simple way of calculating the exchange volume is to use 10% of an infant's estimated blood volume. Serial central hematocrits should be determined every three hours until the hematocrit is stable. A repeat exchange may sometimes be necessary. Some authorities have advocated that the blood volume in these infants be reduced by 10 ml per kg of body weight at the end of a partial exchange transfusion. In view of the fact, however, that newborn infants with polycythemia can be hypovolemic, normovolemic or hypervolemic, this recommendation is not generally accepted.

Available follow-up data suggest that neurologic and developmental abnormalities are more common among infants who have polycythemia. The efficacy of partial exchange transfusion in preventing neonatal complications or reducing neurologic and developmental sequelae is controversial. One reason may be that sludging, microthrombi and pathologic changes may have occurred in utero. Another reason may be that the abnormal sequelae are the result of some underlying pathologic condition. Despite more intense focus on this clinical entity in recent years, more studies are necessary to better define the pathophysiology of the hyperviscosity syndrome.

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Book Reviews

The Western Journal of Medicine *does not review all books sent by publishers, although information about new books received is printed elsewhere in the journal as space permits. Prices quoted are those given by the publishers.*

THAT'S INCURABLE—George Thomas, MD, and Lee Schreiner, MD. Penguin Books, 625 Madison Avenue, New York, NY, 1984. 154 pages, $5.95 (softcover).

As a subject, lethal midline granuloma may well be expected to appear only in textbooks of medicine or to be used on ward rounds by over-zealous residents faced with awe-struck medical students. One does not, however, expect it to appear in a humorous book. In fact, it may seem difficult to imagine how such a topic could even remotely be considered funny. Enter Dr Thomas and Dr Schreiner, pseudonyms for two Harvard physicians who have picked lethal midline granuloma among several horrendous diseases for inclusion in an irreverent and at times hilarious look at modern medicine.

In this book, primarily aimed at the lay public, they tackle a cadre of human maladies with acerbic wit and an eye that is not only jaundiced but in florid hepatic failure. For example, in the chapter "Ten Diseases You Were Better Off Not Knowing About," they describe lethal midline granuloma as a rare disease "that is every bit as bad as it sounds, maybe worse. It is so unpleasant that we would rather not go into details . . . ." The authors take great delight in informing the public of the horrors of rare but lethal diseases, doing so in a style that combines a highly trained medical background with a taste of the macabre. The 11 chapters have titles such as "Common Complaints and the Worst Possible Diseases They Could Represent" and "Life-Threatening Infections You Can Catch From Your Pets." In the latter, for example, they admonish that one way to avoid bubonic plague is to remember "that a rabbit is not a toy. It is a shy, graceful creature that would like to see you swell up and die."

But one question remains: Is this book funny? I believe so. Although sophomoric at times, it will have many of us laughing out loud. As a form of relief from the daily tragedies physicians face, it could do much for our mental hygiene and, as all good works of satire should, it forces us to look at how we practice our art. It is true that some physicians might find this book vulgar and inflammatory. But in view of its cover (the authors are wearing Groucho Marx disguises) it seems unlikely that the easily offended would buy this book in the first place.

The unresolved issue is whether or not a lay person will find this book to be funny. I was disturbed at times by the brutality of the revelations. Is this just more food for worry? Will the average reader be amused or, conversely, terrified by learning that the differential diagnosis of "the sniffles" includes leprosy, syphilis and Wegener's granulomatosis? Yet, the public continues to clamor for books about health. It is only to be expected that satirically striking ones such as this will surface as if to say "OK, folks, you asked for it and now you are going to get it!" Like a pie in the face, how funny it is may depend on which end of the pie one is on.

If laughter is the best medicine, this book will not go down in history as the most efficacious incarnation of that drug. Nonetheless, it is well worth the money for the invigorating effect of a few good chuckles.

BRUCE A. MANN, MD
Department of Medicine
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Albuquerque

* * *

ANKLE INJURIES—Isadore G. Yablon, MD, Professor of Orthopaedic Surgery, Boston University School of Medicine, Boston; David Segal, MD, Professor of Orthopaedic Surgery, Boston University School of Medicine, and Director, Department of Orthopaedic Surgery, Boston City Hospital, Boston, and Robert E. Leach, MD, Professor and Chairman, Department of Orthopaedic Surgery, Boston University School of Medicine, Boston. Churchill Livingstone, Inc., 1560 Broadway, New York, NY 10036, 1983. 264 pages, $15.00.

This excellent book is a welcome addition to the orthopedic literature. The authors have addressed a wide variety of ankle trauma, including ligamentous injury, growth plate injury and fractures, both experimentally and clinically. The stated bias favors an operative approach to fractures, which the authors feel will give more predictable, satisfactory long-term results.

Particularly helpful are the chapters pertaining to initial evaluation, radiographic assessment, bimalleolar, talar dome and plafond fractures, growth plate and ligamentous injuries. The clinical results are often backed by experimental data, which offer a rationale for an approach to treatment. The authors state the problem and support their own treatment preferences by cadaveric and biomechanical studies. The information is presented in a precise and readable format. The bibliography is excellent and serves as a valuable resource.

The book is lacking in a detailed discussion of closed means of treatment for ankle fractures. Certainly there will be times when this form of treatment will be the treatment of choice. More discussion pertaining to chronic ankle pain and instability would have been a useful addition. There is no mention of the treatment problem of the patient who presents with osteopenia associated with an ankle fracture.

The book has a broad appeal. It will be useful to any clinician treating patients with ankle injuries. Orthopedic residents in particular, and family practitioners, emergency room physicians and medical students also should find it a fine reference.

DANIEL OVADIA, MD
Division of Orthopedics and Rehabilitation
The Oregon Health Sciences University
Portland

* * *

SURGERY OF THE KNEE—Edited by John N. Insall, MD, Professor of Orthopedic Surgery, Cornell University Medical Center; Attending Orthopedic Surgeon, The Hospital for Special Surgery and The New York Hospital; Chief of the Knee Service, The Hospital for Special Surgery, New York, and Honorary Consultant Surgeon, The London Hospital, London. Churchill Livingstone, Inc., 1560 Broadway, New York, NY 10036, 1984. 807 pages, $95.00.

This is an excellent basic text for general orthopedists interested in the knee. Its size and detail preclude it being anything other than a reference source for general physicians.

The text is logically organized with anatomy, biomechanics, surgical approaches and then physical and radiographic workup of the knee following. One chapter leads very well into another; however, if a reader is interested in just one aspect of the knee each chapter stands well on its own merit. There is a logical flow to the book that is often missing in multiauthored texts, especially in texts that have such well-known and authoritative coauthors.

The strength of this book lies in Dr John Insall's (the principal author) position in the field of development of reconstructive surgery for the knee. The chapters related to late reconstruction of the adult knee are extremely well done. The weakness of the book is acknowledged in the author's preface and it principally relates to the sections on arthroscopy and reconstruction after athletic-type injuries. In the overall area of knee surgery today, arthroscopy and ligament reconstructive surgery occupy well over half of a general orthopedist's knee practice but occupy less than an eighth of the pages in this text. The author recognizes this in his preface and explains the lack of detail in these two areas on their recent emergence and lack of well-documented studies for operative procedures and techniques currently being employed. Overall, this is an excellent text and is mandatory reading for anyone doing knee surgery, especially adult late reconstructive procedures such as osteotomy and total knee arthroplasty.

HAROLD K. DUNN, MD
Professor and Chairman
Division of Orthopedic Surgery
University of Utah School of Medicine
Salt Lake City

In Memoriam

California Medical Association

BELDING, HIRAM, Riverside. Died August 31, 1984, in Riverside of myocardial infarction, aged 66. Graduate of Northwestern University Medical School, Chicago, 1943. Licensed in California in 1951. Dr Belding was a retired member of the Riverside County Medical Association.

CHEU, HENRY D., San Francisco. Died November 17, 1984, in San Francisco, aged 81. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1929. Licensed in California in 1929. Dr Cheu was a retired member of the San Francisco Medical Society.

DEMETRY, JAMES P., Oroville. Died August 25, 1984, in light plane crash in southwest Wyoming, aged 62. Graduate of the University of Colorado School of Medicine, Denver, 1955. Licensed in California in 1960. Dr DeMetry was a member of the Butte-Glenn Medical Society.

DENKE, REGINALD ERNEST, West Covina. Died August 12, 1984, aged 57. Graduate of Humboldt University Medical School, Berlin, 1951. Licensed in California in 1955. Dr Denke was a member of the Los Angeles County Medical Association.

HINKLEY, WILLIAM, Hayward. Died July 29, 1984, in New Mexico, aged 59. Graduate of the University of Minnesota Medical School, Minneapolis, 1952. Licensed in California in 1952. Dr Hinkley was a member of the Alameda-Contra Costa Medical Association.

HUELSKAMP, MARGARET, San Jose. Died August 22, 1984, in San Jose of a massive brain hemorrhage, aged 68. Graduate of the University of Minnesota Medical School, Minneapolis, 1950. Licensed in California in 1950. Dr Huelskamp was a retired member of the Santa Clara County Medical Society.

HUNNICUTT, LELAND G., Pasadena. Died August 7, 1984, in Pasadena of myocardial infarction, aged 85. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1926. Licensed in California in 1926. Dr Hunnicutt was a retired member of the Los Angeles County Medical Association.

PRASSER, DONALD O., Bakersfield. Died in April 1984 of injuries received in light airplane crash in Walker Basin, aged 72. Graduate of the University of Wisconsin Medical School, Madison, 1941. Licensed in California in 1948. Dr Prasser was an associate member of the Kern County Medical Society.

New Mexico Medical Society

DABBS, WALTER D., Clovis. Died in August 1984 in Clovis, aged 82. Graduate of St Louis University of Medicine, 1926. Licensed in New Mexico in 1927. Dr Dabbs was a member of the DeBaca-Curry-Roosevelt County Medical Society.

HEINE, SIGRID A., Gallup. Died September 28, 1984, in Gallup, aged 45. Graduate of the University of Michigan Medical School, Ann Arbor, 1965. Licensed in New Mexico in 1978. Dr Heine was a member of the McKinley County Medical Society.

SCHWARTZ, LAWRENCE R., Albuquerque. Died in September 1984 in Albuquerque, aged 58. Graduate of the University of Nebraska College of Medicine, Omaha, 1961. Licensed in New Mexico in 1966. Dr Schwartz was a former member of the Albuquerque & Bernalillo County Medical Society and an Associate Member of the New Mexico Medical Society.

WARREN, JAMES WILLIAM, Albuquerque. Died October 14, 1984, in Albuquerque, aged 58. Graduate of the University of Oregon Medical School, Portland, 1954. Licensed in New Mexico in 1958. Dr Warren was a member of the Albuquerque & Bernalillo County Medical Society.

Utah State Medical Association

CURTIS, GEORGE H., Salt Lake City. Died October 20, 1984, in Salt Lake City, aged 72. Graduate of Northwestern University Medical School, Chicago, 1940. Licensed in Utah in 1945. Dr Curtis was a member of the Salt Lake County Medical Society.

GUBLER, JOHN A., Salt Lake City. Died October 1, 1984, in Salt Lake City, age 76. Graduate of Northwestern Medical School, Chicago, 1934. Licensed in Utah in 1937. Dr Gubler was a member of the Salt Lake County Medical Society.

MAVOR, HUNTINGTON, Salt Lake City. Died September 7, 1984, in Salt Lake City, aged 57. Graduate of the University of Rochester School of Medicine and Dentistry, 1955. Licensed in Utah in 1961. Dr Mavor was a member of the Salt Lake County Medical Society.

MCQUARRIE, HARLOW BROOKS, Ephraim-Sanpete. Died October 8, 1984, in Pleasant Grove, aged 76. Graduate of George Washington University School of Medicine, Washington, DC, 1941. Licensed in Utah in 1943. Dr McQuarrie was a member of the Central Utah Medical Society.

ORFANAKIS, MIKE GEORGE, Price. Died August 5, 1984, in Price, aged 42. Graduate of the University of Utah College of Medicine, Salt Lake City, 1967. Licensed in Utah in 1969. Dr Orfanakis was a member of the Salt Lake County Medical Society.

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(Continued on Page 132)

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The Walla Walla Clinic, a 30 physician multi-specialty Clinic, is nestled in the foothills of Southeastern Washington's Blue Mountains. Walla Walla serves an immediate county of 60,000 with a referral population of 150,000 people. Walla Walla is a sophisticated regional medical center with most medical and surgical subspecialties, and outstanding technological support (CAT scanning, digital angiography, nuclear medicine, ultrasonography).

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(Continued on Page 128)

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(Continued from Page 126)

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ASSOCIATE NEEDED to join female General Practitioner, West San Fernando Valley (West Los Angeles County). Willing to wait for the right person. Contact: Serena M. Friedman, MD, (818) 702-9962.

ALASKA: Family Practitioner, Board eligible/certified, to join the Fairbanks office of Alaska's largest multi-specialty clinic. Generous guaranteed salary, benefits, and relocation allowance. Partnership opportunity. Contact: Administrator, Fairbanks Clinic, 1867 Airport Rd, Fairbanks, AK 99701.

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(Continued on Page 130)

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America's declining productivity is serious business.

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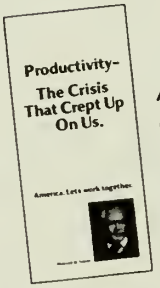

America's productivity growth rate has been slipping badly for several years now, compared to that of other nations. And it's adversely affecting each and every one of us.

We've all seen plants and businesses close down. Tens of thousands of jobs lost. Prices rising, quality deteriorating. A flood of foreign-made products invading our shores. It's all part of our declining productivity rate.

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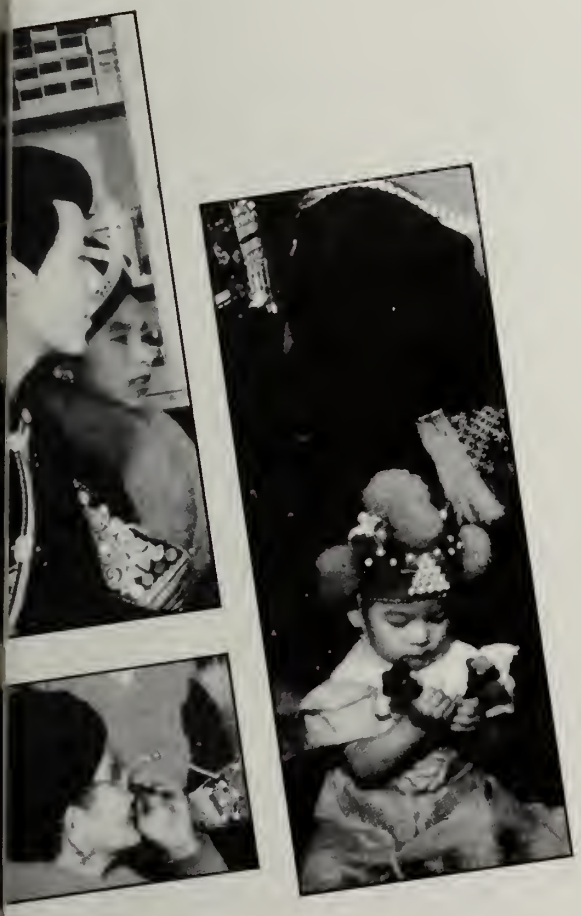

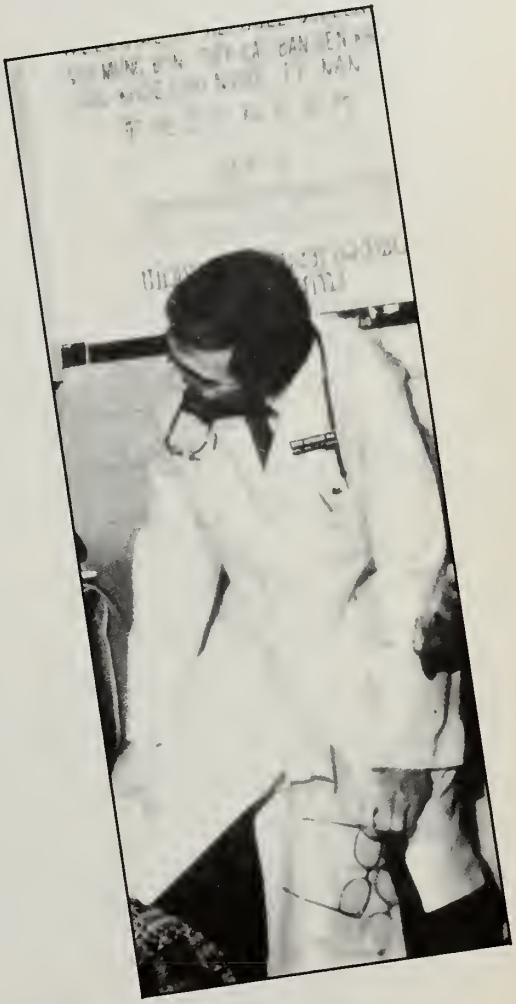

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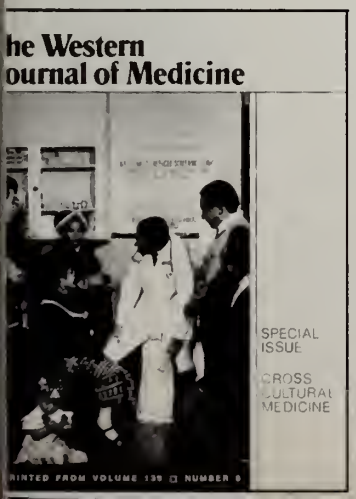

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(Continued from Page 124)

February 13-15—**Clinical Laboratory Molecular Analysis: Future Direction.** Scripps Clinic and Research Foundation at Vacation Village San Diego. 21 hrs. Contact: Dianne Tisue, Scripps Clinic, 10666 North Torrey Pines Rd., La Jolla 92037. (619) 457-8556.

February 22-23—**American College of Physicians: 1985 Regional Scientific CME Meeting.** ACP at Doubletree Inn, Monterey. Friday-Saturday. Contact: Jerry P. Lewis, MD, 618 Francisco Place, Davis 95616.

February 23-24—**Expanding Horizons.** UCSF at Golden Gateway Holiday Inn, San Francisco. Saturday-Sunday. Contact: UCSF.

February 28-March 2—**California Medical Association Postgraduate Institute.** Curry Village, Yosemite. Thursday-Saturday. Contact: CMA, 44 Gough St., San Francisco 94103-1233. (415) 863-5522.

March 1—**11th Annual Diabetes Program.** UCD. Friday.

March 2-3—**San Francisco Academy of Hypnosis Annual Workshop** at Letterman Army Medical Center, San Francisco. Saturday-Sunday. 28 hrs. Fee: $300. Contact: Jan Brooks, SFAH, 2820 15th Ave., San Francisco, CA 94114.

March 3-6—**Maxillofacial Trauma.** UCSF at Hyatt Lake Tahoe, Incline Village. Sunday-Wednesday.

March 6-8—**35th Annual Course for Physicians in Family Practice.** Mount Zion Hospital and Medical Center, San Francisco. Wednesday-Friday. Contact: Robin Jackson, Office of Continuing Education, PO Box 7921, San Francisco 94115. (415) 885-7269.

March 7-10—**Dermatologic Survey: State of the Art.** UCSF at Incline Village, Nevada. Thursday-Sunday. Fee: $400.

March 8-13—**California Medical Association Annual Session** at Town and Country Hotel, San Diego. Friday-Wednesday. Contact: Barbara Smart, CMA, 44 Gough St., San Francisco 94103-1233. (415) 863-5522, ext. 404.

March 10-13—**New Strategies for Common Clinical Problems.** UCSF at Granlibakken Ski and Raquet Resort, Tahoe City. Sunday-Wednesday.

March 13-17—**Orthopaedic Symposium.** UCD at Silverado Country Club, Napa. Wednesday-Sunday.

March 14-16—**New Approaches to the Diagnosis and Treatment of Diseases of the Elderly.** Annenberg Center for Health Science. Thursday-Saturday. Contact: Annenberg Center for Health Science, Eisenhower Medical Center, 39000 Bob Hope Dr., Rancho Mirage 92270.

March 15-23—**Reider Laser Center Symposium.** UCI. One week.

March 20-22—**Advances and Controversies in Bronchial Asthma.** California Thoracic Society at Marriott's Santa Barbara Biltmore Hotel, Santa Barbara. Wednesday-Friday. Contact: Medical Education Director, California Thoracic Society, 424 Pendleton Way, Oakland 94621. (415) 638-5864.

March 21-22—**Current Practices in Diagnosis & Treatment of Arthritis—Connective Tissues and Musculoskeletal Diseases.** Palo Alto Medical Foundation at St. Francis Hotel, San Francisco. Thursday-Friday. 12 hrs. Contact: Palo Alto Medical Foundation, 385 Homer Ave, Palo Alto, 94301.

March 22-23—**Cancer and Sexuality Postgraduate Institute.** California Medical Association at Marriott Inn, Marina del Rey. Friday-Saturday. Contact: CMA, 44 Gough St, San Francisco 94103-1233. (415) 863-5522.

March 25-29—**Family Practice Refresher Course—1985.** UCSD at Palm Springs Spa Hotel. Monday-Friday. 30 hrs.

March 29-31—**Office Emergencies in Primary Care.** Continuing Medical Education Associates at Hotel Del Coronado, San Diego. Friday-Sunday. 18 hrs. Fee: $275. Contact: Jackie Shiller, CMEA, PO Box 84296, San Diego 92138. (619) 223-2997.

April 8-11—**Diabetes Mellitus: Modern Management Methods.** LLU at Maui Marriott, Maui. Monday-Wednesday. 16 hrs.

April 17-21—**Mountain Medicine: 1985.** UCD at North Lake Tahoe. Wednesday-Sunday.

April 24-28—**Annual Scientific Program and Postgraduate Course.** Pacific Coast Fertility Society at Caesars Palace, Las Vegas. Wednesday-Sunday. 23 hrs. Contact: Pacific Coast Fertility Society, 5820 Wilshire Blvd., #500, Los Angeles 90036. (213) 937-5514.

April 27-28—**13th Annual Family Practice Symposium.** Southern Permanente Group at Disneyland Hotel, Anaheim. Friday-Saturday. 11 hrs. Contact: Southern California Kaiser Permanente Group, 4747 Sunset Blvd, Los Angeles 90027.

(Continued on Page 135)

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References:
1. Strauss WE, McIntyre KM, Parisi AF, et al: Safety and efficacy of diltiazem hydrochloride for the treatment of stable angina pectoris: Report of a cooperative clinical trial. Am J Cardiol 49:560-566, 1982.
2. Pool PE, Seagren SC, Bonanno JA, et al: The treatment of exercise-inducible chronic stable angina with diltiazem: Effect on treadmill exercise. Chest 78 (July suppl):234-238, 1980.

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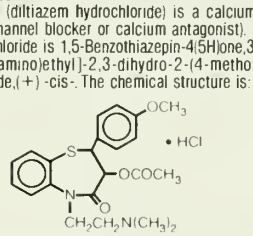

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Hemodynamic and Electrophysiologic Effects. Like other calcium antagonists, diltiazem decreases sinoatrial and atrioventricular conduction in isolated tissues and has a negative inotropic effect in isolated preparations. In the intact animal, prolongation of the AH interval can be seen at higher doses.

In man, diltiazem prevents spontaneous and ergonovine-provoked coronary artery spasm. It causes a decrease in peripheral vascular resistance and a modest fall in blood pressure and, in exercise tolerance studies in patients with ischemic heart disease, reduces the heart rate-blood pressure product for any given work load. Studies to date, primarily in patients with good ventricular function, have not revealed evidence of a negative inotropic effect; cardiac output, ejection fraction, and left ventricular end diastolic pressure have not been affected. There are as yet few data on the interaction of diltiazem and beta-blockers. Resting heart rate is usually unchanged or slightly reduced by diltiazem.

Intravenous diltiazem in doses of 20 mg prolongs AH conduction time and AV node functional and effective refractory periods approximately 20%. In a study involving single oral doses of 300 mg of CARDIZEM in six normal volunteers, the average maximum PR prolongation was 14% with no instances of greater than first-degree AV block. Diltiazem-associated prolongation of the AH interval is not more pronounced in patients with first-degree heart block. In patients with sick sinus syndrome, diltiazem significantly prolongs sinus cycle length (up to 50% in some cases).

Chronic oral administration of CARDIZEM in doses of up to 240 mg/day has resulted in small increases in PR interval, but has not usually produced abnormal prolongation. There were, however, three instances of second-degree AV block and one instance of third-degree AV block in a group of 959 chronically treated patients.

Pharmacokinetics and Metabolism. Diltiazem is absorbed from the tablet formulation to about 80% of a reference capsule and is subject to an extensive first-pass effect, giving an absolute bioavailability (compared to intravenous dosing) of about 40%. CARDIZEM undergoes extensive hepatic metabolism in which 2% to 4% of the unchanged drug appears in the urine. In vitro binding studies show CARDIZEM is 70% to 80% bound to plasma proteins. Competitive ligand binding studies have also shown CARDIZEM binding is not altered by therapeutic concentrations of digoxin, hydrochlorothiazide, phenylbutazone, propranolol, salicylic acid, or warfarin. Single oral doses of 30 to 120 mg of CARDIZEM result in detectable plasma levels within 30 to 60 minutes and peak plasma levels two to three hours after drug administration. The plasma elimination half-life following single or multiple drug administration is approximately 3.5 hours. Desacetyl diltiazem is also present in the plasma at levels of 10% to 20% of the parent drug and is 25% to 50% as potent a coronary vasodilator as diltiazem. Therapeutic blood levels of CARDIZEM appear to be in the range of 50 to 200 ng/ml. There is a departure from dose-linearity when single doses above 60 mg are given; a 120-mg dose gave blood levels three times that of the 60-mg dose. There is no information about the effect of renal or hepatic impairment on excretion or metabolism of diltiazem.

INDICATIONS AND USAGE

1. **Angina Pectoris Due to Coronary Artery Spasm.** CARDIZEM is indicated in the treatment of angina pectoris due to coronary artery spasm. CARDIZEM has been shown effective in the treatment of spontaneous coronary artery spasm presenting as Prinzmetal's variant angina (resting angina with ST-segment elevation occurring during attacks).
2. **Chronic Stable Angina (Classic Effort-Associated Angina).** CARDIZEM is indicated in the management of chronic stable angina. CARDIZEM has been effective in controlled trials in reducing angina frequency and increasing exercise tolerance.

There are no controlled studies of the effectiveness of the concomitant use of diltiazem and beta-blockers or of the safety of this combination in patients with impaired ventricular function or conduction abnormalities.

CONTRAINDICATIONS

CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker, and (3) patients with hypotension (less than 90 mm Hg systolic).

WARNINGS

1. **Cardiac Conduction.** CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (six of 1243 patients for 0.48%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.
2. **Congestive Heart Failure.** Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). Experience with the use of CARDIZEM alone or in combination with beta-blockers in patients with impaired ventricular function is very limited. Caution should be exercised when using the drug in such patients.
3. **Hypotension.** Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.
4. **Acute Hepatic Injury.** In rare instances, patients receiving CARDIZEM have exhibited reversible acute hepatic injury as evidenced by moderate to extreme elevations of liver enzymes. (See PRECAUTIONS and ADVERSE REACTIONS.)

PRECAUTIONS

General. CARDIZEM (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any new drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Drug interaction. Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM (See WARNINGS).

Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers or digitalis is usually well tolerated. Available data are not sufficient, however, to predict the effects of concomitant treatment, particularly in patients with left ventricular dysfunction or cardiac conduction abnormalities. In healthy volunteers, diltiazem has been shown to increase serum digoxin levels up to 20%.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response in in vitro bacterial tests. No intrinsic effect on fertility was observed in rats.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

There are no well-controlled studies in pregnant women; therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when CARDIZEM is administered to a nursing woman if the drug's benefits are thought to outweigh its potential risks in this situation.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded.

In domestic placebo-controlled trials, the incidence of adverse reactions reported during CARDIZEM therapy was not greater than that reported during placebo therapy.

The following represent occurrences observed in clinical studies which can be at least reasonably associated with the pharmacology of calcium influx inhibition. In many cases, the relationship to CARDIZEM has not been established. The most common occurrences, as well as their frequency of presentation, are: edema (2.4%), headache (2.1%), nausea (1.9%), dizziness (1.5%), rash (1.3 asthenia (1.2%), AV block (1.1%). In addition, the following ev were reported infrequently (less than 1%) with the order of prese tion corresponding to the relative frequency of occurrence.

Cardiovascular	Flushing, arrhythmia, hypotension, brady dia, palpitations, congestive heart fail syncope.
Nervous System	Paresthesia, nervousness, somnole tremor, insomnia, hallucinations, and amne
Gastrointestinal:	Constipation, dyspepsia, diarrhea, vomit mild elevations of alkaline phosphatase, S SGPT, and LDH.
Dermatologic:	Pruritus, petechiae, urticaria, photosensiti
Other:	Polyuria, nocturia.

The following additional experiences have been noted:

A patient with Prinzmetal's angina experiencing episodes vasospastic angina developed periods of transient asymptom asystole approximately five hours after receiving a single 60 dose of CARDIZEM.

The following postmarketing events have been reported in quently in patients receiving CARDIZEM: erythema multiforme; kopenia; and extreme elevations of alkaline phosphatase, S SGPT, LDH, and CPK. However, a definitive cause and effect betw these events and CARDIZEM therapy is yet to be established.

OVERDOSAGE OR EXAGGERATED RESPONSE

Overdosage experience with oral diltiazem has been limi Single oral doses of 300 mg of CARDIZEM have been well toler by healthy volunteers. In the event of overdosage or exaggera response, appropriate supportive measures should be employe addition to gastric lavage. The following measures may be conside

Bradycardia	Administer atropine (0.60 to 1.0 mg). If th is no response to vagal blockade, admini isoproterenol cautiously.
High-Degree AV Block	Treat as for bradycardia above. Fixed hi degree AV block should be treated with diac pacing.
Cardiac Failure	Administer inotropic agents (isoproter dopamine, or dobutamine) and diuretics.
Hypotension	Vasopressors (eg, dopamine or levarter bitartrate).

Actual treatment and dosage should depend on the severity of clinical situation and the judgment and experience of the trea physician.

The oral/LD_{50}'s in mice and rats range from 415 to 740 mg and from 560 to 810 mg/kg, respectively. The intravenous LD_{50} these species were 60 and 38 mg/kg, respectively. The oral LD_{5} dogs is considered to be in excess of 50 mg/kg, while lethality seen in monkeys at 360 mg/kg. The toxic dose in man is not kno but blood levels in excess of 800 ng/ml have not been associa with toxicity.

DOSAGE AND ADMINISTRATION

Exertional Angina Pectoris Due to Atherosclerotic Co nary Artery Disease or Angina Pectoris at Rest Due to Co nary Artery Spasm. Dosage must be adjusted to each patie needs. Starting with 30 mg four times daily, before meals an bedtime, dosage should be increased gradually (given in divi doses three or four times daily) at one- to two-day intervals u optimum response is obtained. Although individual patients r respond to any dosage level, the average optimum dosage ra appears to be 180 to 240 mg/day. There are no available data con ing dosage requirements in patients with impaired renal or hep function. If the drug must be used in such patients, titration should carried out with particular caution.

Concomitant Use With Other Antianginal Agents:

1. **Sublingual NTG** may be taken as required to abort ac anginal attacks during CARDIZEM therapy.
2. **Prophylactic Nitrate Therapy**—CARDIZEM may be sa coadministered with short- and long-acting nitrates, but th have been no controlled studies to evaluate the antiang effectiveness of this combination.
3. **Beta-blockers.** (See WARNINGS and PRECAUTIONS.)

HOW SUPPLIED

Cardizem 30-mg tablets are supplied in bottles of 100 (N 0088-1771-47) and in Unit Dose Identification Paks of 100 (N 0088-1771-49). Each green tablet is engraved with MARION on side and 1771 engraved on the other. CARDIZEM 60-mg sco tablets are supplied in bottles of 100 (NOC 0088-1772-47) and in U Dose Identification Paks of 100 (NOC 0088-1772-49). Each yel tablet is engraved with MARION on one side and 1772 on the ot

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(Continued from Page 132)

ALASKA

June 8-11—**Alaska State Medical Association—Annual Meeting.** Haines. Saturday-Tuesday. Contact: ASMA, 4107 Laurel St., Anchorage 99504. (907) 562-2662.

IDAHO

February 16-23—**Internal Medicine.** University of Washington School of Medicine at Elkhorn Resort, Sun Valley. One week. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

February 17-22—**11th Stanford-Palo Alto Medical Foundation Research Institute Winter Course in Infectious Diseases.** Sun Valley. Sunday-Friday. Contact: Registrar, American College of Physicians, 4200 Pine St., Philadelphia, PA 19104.

February 23-March 2—**Office Orthopaedics.** University of Washington School of Medicine at Elkhorn Resort, Sun Valley. One week. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

March 2-9—**Electromyography.** University of Washington School of Medicine at Elkhorn Resort, Sun Valley. One week. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

MONTANA

February 20-23—**Big Sky Pulmonary/Ski Conference.** American Lung Association of Montana at Big Sky of Montana. Wednesday-Saturday. Contact: ALA of Montana, 825 Helena Ave., Helena 59601. (406) 442-6556.

NEW MEXICO

Information, requests for accreditation and items to be listed should be sent to the chairman of the CME Committee, New Mexico Medical Society, 303 San Mateo NE, Suite 204, Albuquerque, NM 87108 at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 266-7868.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

January 18-19—**Carrie Tingley Hospital 15th Winter Orthopaedic Seminar.** Albuquerque. 10 hrs. AMA Cat. I. Friday-Saturday. Hilton Inn. Contact: Office of Medical Affairs, Carrie Tingley Hospital, PO Box 25447, Albuquerque 87125. (505) 841-9121.

January 23-27—**New Mexico Metabolism Symposium.** Taos. Wednesday-Sunday. Tennis Ranch. 12 hrs. AMA Cat. I. Contact: Office of CME, Lovelace Medical Center, 5400 Gibson SE, Albuquerque 87106. (505) 262-7353.

February 1-3—**Advances in Internal Medicine V.** Albuquerque. Friday-Sunday. 15 hrs. AMA Cat. I. Veterans Administration Medical Center. Contact: Office of CME, UNM SOM, Albuquerque 87131. (505) 277-3942.

February 4-8—**Alta Medical Conference.** Alta, Utah. Monday-Friday. 10 hrs. AMA Cat. I. Contact: New Mexico Mid-Winter Study Group, 717 Encino Pl. NE, #9, Albuquerque 87102. (505) 842-6762.

February 14-15—**Cardiovascular Ultrasonic Flowmetry.** Albuquerque. Thursday-Friday. 11½ hrs. AMA Cat. I. Contact: Lovelace Medical Foundation, 5400 Gibson Blvd. SE, Albuquerque 87108. (505) 262-7155.

February 15-16—**Heal Thyself—A Seminar Focusing on Quality of Life and Caring for Others.** Albuquerque. Friday-Saturday. Clarion Four Seasons. 11 hrs. AMA Cat. I. Contact: Office of CME, Presbyterian Hospital, Albuquerque 87102. (505) 841-1225.

February 21-23—**18th Annual OB/GYN Postgraduate Seminar.** Albuquerque. Thursday-Saturday. AMFAC Hotel. 15 hrs. AMA Cat. I. Contact: Office of CME, UNM SOM, Albuquerque 87131. (505) 277-3942.

(Continued on Page 140)

INFORMATION FOR AUTHORS

Submitting Manuscripts

Manuscripts for consideration should be sent to the editor, Malcolm S. M. Watts, MD, 44 Gough Street, San Francisco, California 94103. The transmittal letter should designate one person as correspondent and include complete address, with ZIP code and telephone number.

In view of *The Copyright Revision Act of 1976,* transmittal letters should contain the following language: "In consideration for reviewing and editing my submission, the author(s) undersigned hereby transfers, assigns or otherwise conveys all copyright ownership to THE WESTERN JOURNAL OF MEDICINE in the event that such work is published by the journal." This statement should be signed by *all* the authors.

Authors are urged to seek clarity and succinctness in all manuscripts regardless of subject matter or format and to give close attention to syntax, grammar and spelling.

Clinical Investigation Section

Articles that authors wish to have considered for the Clinical Investigation section should be so designated in the transmittal letter. The type of articles appropriate for this section are those that describe experimental work in humans that extensively and prospectively examines scientific hypotheses relating to disease. An article describing a single case report will not normally be considered appropriate for this section.

Preparing Manuscripts

The original manuscript and *two* copies should be submitted on heavy bond paper (8½ by 11 inches, *not* erasable), typed *double-spaced throughout* (including legends, tables and references) on one side of the paper, with 1½-inch margins. Ordinarily, articles should not exceed 3,000 words (less than 15 text pages, typed double-spaced). Under exceptional circumstances only will articles longer than 4,000 words be published. Pages should be numbered consecutively, beginning with the title page.

Style

Abbreviations. Use of abbreviations should be minimized. If they are necessary, abbreviations should be spelled out at first mention, with the abbreviation itself immediately following in parentheses.

Weights and measures. All measurements should be given in metric units. English equivalents should be given parenthetically if the measurements were originally done in English units.

Temperatures. Temperature readings should be given first in Celsius, followed by the Fahrenheit equivalent in parentheses.

Drug names. If the trade name of a drug is used, the generic name should be given first, followed by the trade name in parentheses. Trade names are capitalized, generic names are not.

Title Page

Titles are best when brief and concise. The title page should include the full name of the author(s), with degrees, academic or professional titles, complete addresses and any institutional or other affiliations. The complete name and address of the person who will handle reprint requests also should appear on this page.

Abstract

The abstract (approximately 150 words) should be a short summary, saying in brief what is said at length in the body of the article—rather than such and such "is discussed," "is presented" or "was investigated."

Tables and Figures

Tables

Each table should be typed on a separate sheet of paper, be numbered consecutively in Arabic numerals, have a brief descriptive title and have its position indicated in the text.

Illustrations (Figures)

Three sets of clear, unmounted black and white glossy prints of figures should be submitted (preferably 5 by 7 inches, but no larger than 8½ by 11 inches). For line drawings, original artwork or glossy prints are acceptable. Illustrations should be numbered consecutively in Arabic numerals and their position indicated in the text. Figure number, first author's name and top of the photo should be shown on the reverse side of each illustration. Recognizable photographs of patients are to be masked and written permission for publication obtained from the patients.

Legends

All legends for figures should be typed together on a separate sheet of paper. Magnification and stain for photomicrographs should be indicated in parentheses.

Permission for Reproduction

If an illustration or table has been used previously in another publication, written permission for its use must be obtained from the publisher, and should accompany the manuscript. The source should be acknowledged in the legend if it can be done briefly by citation of a reference number. Otherwise, acknowledgment is made at the end of the figure legend or at the bottom of the table.

References

References should be limited to those cited in the text. They must be typed double-spaced and numbered consecutively as they appear in the manuscript. (See examples below for style.) Abbreviations of journal titles should conform to those used in *Index Medicus.*

Journal Articles

Note handling of multiple authorship. If more than three authors are listed as contributors, use "et al" to designate those names after the first three. Also note capitalization, punctuation, mention of inclusive page numbers and year of publication. Separate the subtitle from the title by either a dash or a colon. Use colon *only* if it appears in the original citation.

1. Jones JS, Anderson HW, Johnson DW, et al: The athletic heart revisited—Sudden death of a 28-year-old athlete. JAMA 1978; 292:444-456

2. Graybill JR, Alford RH, Smith RG, et al: Cell-mediated immunity in cryptococcosis: A brief review. Cell Immunol 1978; 7:76-79

Books

Note handling of "edition," "editor(s)," and "volume," as well as appropriate sequence of reference information and capitalization of chapters and titles.

3. Berne EJ, Smith TL: Role playing in therapy, chap 2, Principles of Group Therapy. New York, Oxford University Press, 1966, pp 35-51 *(author of chapter same as author of book)*

4. Munsung JM: The role of drugs, chap 2, *In* Brest AN, Mayer JH (Eds): Hypertension—Vol 2, Therapy, 2nd Ed. Springfield, Ill, Charles C Thomas, 1961, pp 456-479 *(author of chapter different from authors of book)*

Pamphlets, Monographs or Books With No Given Author

5. AMA Department of Drugs: AMA Drug Evaluation, 3rd Ed. Littleton, Mass, Publishing Sciences Group, 1977 *(corporate author)*

6. Compilation of Standard Definitions, 3rd Ed. Philadelphia, American Society for Testing and Materials, 1976 *(no given author; give name and place of publisher)*

Articles in Press or Accepted for Publication

Any article accepted for publication should include the name of the journal (appropriately abbreviated) in which it will appear, and the phrase "in press" or "accepted for publication" in place of the date of publication.

Personal Communications and Unpublished Data

This information should *not* be included in the reference list but should be given in parentheses in the body of the text. Date of communication, whether it was personal or written, and the person's name, highest academic degree and professional affiliation should be provided.

Acknowledgments

It is the policy of the *WJM* not to print acknowledgments, the feeling being that if a person has contributed enough to a paper to be mentioned, he or she should be included among the authors, or the contribution should be mentioned in the body of the paper or in a footnote.

Correspondence

Brief manuscripts commenting on articles that have appeared in the journal, containing information of interest to physicians or discussing issues of the day will be considered for publication. Very short reports of cases, clinical experience, clinical studies, adverse effects and the like also will be considered. Items for the Correspondence section should not exceed 600 words and should have no more than five bibliographic references and one figure or table.

Author Responsibility

Authors are responsible for all statements made in articles. Manuscripts are considered for publication with the explicit understanding that they are original, have not been published previously and are not simultaneously under consideration by any other publication.

All accepted manuscripts are subject to copy editing, and authors are sent edited galleys for approval. No changes will be made after the final, edited version has been approved by the author.

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(Continued from Page 135)

February 22-24—**13th Annual Taos Lung Disease Symposium.** Taos. Friday-Sunday. Kachina Lodge. 12 hrs. AMA Cat. 1. Contact: New Mexico Chapter, American Thoracic Society, 216 Truman NE, Albuquerque 87108. (505) 265-0732.

February 28-March 2—**First Ruidoso Heart Seminar—Practical Cardiology.** Ruidoso. Thursday-Saturday. Inn of the Mountain Gods. Contact: NM Heart Association, 2403 San Mateo NE, Albuquerque 87108. (505) 268-3711.

March 8-10—**Arthritis Foundation Symposium and Harris Galante Hip Replacement Workshop.** Albuquerque. Friday-Sunday. AMFAC Hotel. Contact: The Arthritis Foundation, 5112 Grand Avenue NE, Albuquerque 87106. (505) 265-1545.

March 15-16—**Primary Care Orthopaedics.** Albuquerque. Friday-Saturday. AMFAC Hotel. 15 hrs. AMA Cat. I. Contact: Office of CME, UNM SOM, Albuquerque 87131. (505) 277-3942.

April 11-13—**Seventh Annual Pediatric Cardio-Pulmonary Update.** Thursday-Saturday. AMFAC Hotel. 15 hrs. AMA Cat. I. Contact: Office of CME, UNM SOM, Albuquerque 87131. (505) 277-3942.

OREGON

The following list of continuing medical offerings in the state of Oregon is compiled by the Oregon Medical Association's Council on Medical Education. If you wish to submit information regarding future postgraduate courses, please submit the information to James A. Kronenberg, Associate Executive Director, Oregon Medical Association, 5210 SW Corbett Ave., Portland, OR 97201, or phone (503) 226-1555.

MEDICAL GRAND ROUNDS

Douglas Community Hospital, 738 West Harvard Avenue, Roseburg 97470:

Every Monday, 12:30 p.m. Contact: Robert A. Driver, MD, Douglas Community Hospital, 738 West Harvard Avenue, Roseburg, OR 97470. (503) 673-6641.

Emanuel Hospital, 2801 N. Gantenbein Street, Portland 97227:

Every Friday, 8:00 a.m. to 9:00 a.m. **Medical Grand Rounds.** Contact: Philipa McClure, Emanuel Hospital, 2801 N. Gantenbein Street, Portland, OR 92227. (505) 280-3200.

Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland 97210:

Every Wednesday, 8:00 a.m. to 9:00 a.m. **Medicine Grand Rounds.** Nursing Education Building, Room 110. Contact: Department of Medicine, Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland, OR 97201. (503) 229-7454.

Providence Medical Center, 4805 NE Glisan, Portland 97213:

Every Wednesday, 8:00 a.m. **Medical Grand Rounds.** Contact: Richard Wernick, MD, Providence Medical Center, 4805 NE Glisan, Portland, OR 97213. (503) 230-6085.

Sacred Heart General Hospital, 1200 Alder Street, Eugene, OR 97440:

Every Tuesday, 8:00 a.m. to 9:00 a.m. **Medical Grand Rounds.** Hospital Auditorium. Contact: Medical Education Committee. PO Box 10905, Eugene, OR 97440.

Salem Hospital, 665 Winter Street SE, Salem 97301:

First and third Thursday of each month 7:15 a.m. to 8:15 a.m. **Medical Live Audit Conference.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter Street SE, Salem, OR 97301. (503) 370-5339.

Every Friday, 7:30 a.m. to 8:30 a.m. **Friday Grand Rounds.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter Street SE, Salem, OR 97301. (503) 370-5339.

St. Vincent Hospital & Medical Center, 9205 SW Barnes Road, Portland 97225:

First, third, fourth and fifth Wednesday of each month, 8:00 a.m. to 9:00 a.m. **Medical Grand Rounds.** Souther Auditorium. Contact: Bonnie Conger, Secretary to Dr Kenneth Melvin, St. Vincent Hospital & Medical Center, 9205 SW Barnes Road, Portland 97225. (503) 297-4411, Ext. 2230

Oregon Health Sciences University, Department of Psychiatry, Portland 97201:

Every Wednesday, 4:00 p.m. to 5:00 p.m. **Department of Psychiatry Grand Round Presentations.** Room 8B-60, University Hospital South,

CONTACT INFORMATION

OHSU-CME—Contact: Division of Continuing Medical Education, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8700.

Oregon Health Sciences University. Contact: Dept. of Psychiatry, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8144.

Oregon Health Sciences University, Department of Medicine, Portland 97201:

Every Tuesday, 8:00 a.m. to 9:00 a.m. **Department of Medicine Grand Rounds.** U.H.S.-8B-60, Oregon Health Sciences University. Contact: Dept. of Medicine, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8607.

FAMILY PRACTICE GRAND ROUNDS

Every Wednesday, 11:00 a.m. to 12:00 Noon. **Family Practice Grand Rounds.** Family Practice Center, Oregon Health Sciences University, Portland. Contact: William A. Fisher, MD, Oregon Health Sciences University, Department of Family Practice, Portland, OR 97201. (503) 225-7590.

DERMATOLOGY

March 27-28—**Dermatopathology Conference.** Portland. Wednesday-Thursday. Marriott Hotel. Contact: OHSU-CME.

FAMILY PRACTICE

February 11-15—**Family Practice Review Program.** Portland. Monday-Tuesday. Marriott Hotel. Contact: OHSU-CME.

March 1-2—**Difficult Problems in Surgery.** Portland. Friday-Saturday. Red Lion Lloyd Center. Contact: OHSU-CME.

PATHOLOGY

March 27-28—**Dermatopathology Conference.** Portland. Wednesday-Thursday. Marriott Hotel. Contact: OHSU-CME.

SURGERY

March 1-2—**Difficult Problems in Surgery.** Portland. Friday-Saturday. Red Lion Lloyd Center. Contact: OHSU-CME.

OF INTEREST TO ALL PHYSICIANS

February 10—**Alcohol and Drug Symposium.** Portland. Sunday. Marriott Hotel. Contact: OHSU-CME.

February 28-March 3—**Update in Rheumatology—1985.** Bend. Thursday-Sunday. Inn of the Seventh Mountain. Contact: OHSU-CME.

April 11-12—**Sommer Memorial Lectures.** Portland. Thursday-Friday. OHSU Library Auditorium. Contact: OHSU-CME.

May 10—**Hypertension.** Portland. Friday. OHSU Library Auditorium. Contact: OHSU-CME.

May 31-June 1—**Internal Medicine Update.** Portland. Friday-Saturday. Marriott Hotel. Contact: OHSU-CME.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah State Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. They also must meet the definition of Utah Approved CME Credit for the purpose of medical license reregistration in Utah. Accredited institutions wishing to list AMA Category 1/Utah Approved CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, Utah 84102; or phone (801) 355-5290. For information on CME accreditation or on the CME requirements of the Utah Physicians' Licensing Board, please write the CME office at the above address.

(Continued on Page 143)

SPONSORS OF COURSES—ABBREVIATIONS

AF: Arthritis Foundation, 1174 East 2700 South, Salt Lake City 84117. (801) 466-9389.

CH: Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price, UT 84501. (801) 637-4800.

CWH: Cottonwood Hospital, 5770 South 300 East, Salt Lake City 84101. (801) 262-3461.

FHP: Family Health Program/Utah, 323 South Sixth East, Salt Lake City 84102. (801) 335-1234. Contact: Kay Schultz for course information.

HAFB: Hill Air Force Hospital, Hill Air Force Base 84406. (801) 777-1262.

HCH: Holy Cross Hospital, 1045 East First South, Salt Lake City 84102. (801) 350-4744.

LDSH: Latter-Day Saints Hospital, 325 8th Avenue, Salt Lake City 84143. (801) 350-1100.

MDH: McKay-Dee Hospital Center, 3939 Harrison Blvd., Ogden 84409. (801) 399-4141.

OEH: Rocky Mountain Center for Occupational and Environmental Health, 50 North Medical Drive, Salt Lake City 84132. (801) 581-8719.

OSS: Ogden Surgical Society, PO Box 9311, Ogden 84409.

PCMC: Primary Children's Medical Center, 320 12th Ave., Salt Lake City 84103. (801) 363-1221.

SHCC: Shriners Hospital for Crippled Children, Intermountain Unit, Fairfax Ave. at Virginia St., Salt Lake City 84103. (801) 532-5307.

SLSC: Salt Lake Surgical Center, 617 East 3900 South, Salt Lake City 84117. (801) 261-3141.

UAFP: Utah Academy of Family Physicians, 1146 Westminster Ave., Salt Lake City 84105. (801) 466-9478.

UUMC: University of Utah Medical Center, 50 North Medical Drive, Salt Lake City 84132. (801) 581-2258.

USMA: Utah State Medical Association, 540 East Fifth South, Salt Lake City 84102. (801) 355-7477.

UVH: Utah Valley Hospital, 1034 North Fifth West, Provo 84601. (801) 373-7850.

VAMC: Veterans Administration Medical Center, 500 Foothill Drive, Salt Lake City 84148. (801) 582-1565.

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Brief Summary of prescribing information

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INDICATIONS AND USAGE: Ru-Tuss Tablets provide relief of the symptoms resulting from irritation of sinus, nasal and upper respiratory tract tissues.

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OVERDOSAGE: Since the action of sustained release products may continue for as long as 12 hours, treatment of overdoses directed at reversing the effects of the drug and supporting the patient should be maintained for at least that length of time. Saline cathartics are useful for hastening evacuation of unreleased medication. In children and infants, antihistamine overdosage may produce convulsions and death.

ADVERSE REACTIONS: Hypersensitivity reactions such as rash, urticaria, leukopenia agranulocytosis, and thrombocytopenia may occur. Other adverse reactions to Ru-Tuss Tablets may be drowsiness, lassitude, giddiness, dryness of the mucous membranes, tightness of the chest, thickening of bronchial secretions, urinary frequency and dysuria, palpitation, tachycardia, hypotension/hypertension, faintness, dizziness, tinnitus, headache, incoordination, visual disturbances, mydriasis, xerostomia, blurred vision, anorexia, nausea, vomiting, diarrhea, constipation, epigastric distress, hyperirritability, nervousness, dizziness and insomnia. Large overdoses may cause tachypnea, delirium, fever, stupor, coma and respiratory failure.

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Federal law prohibits dispensing without prescription.

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Pioneers in medicine for the family

(Continued from Page 141)

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution or the CME office for current details.

MEDICAL GRAND ROUNDS

Each Wednesday—8:00-9:00 a.m. Alternating between University of Utah Medical Center and VA Medical Center, Salt Lake City. Contact: William D. Odell, MD, PhD, Professor and Chairman, Dept. of Internal Medicine, Univ. of Utah, (801) 581-7606.

* * *

February 9-16—**8th Annual Update in Clinical Microbiology/Immunology** (Sponsor: University of Utah). Saturday-Saturday. Park City. Fee to be announced. 25 hrs. Contact: John Matsen, MD, (801) 581-7480.

February 12-15—**14th Annual Family Practice Refresher Course** (Sponsor: University of Utah). Tuesday-Friday. Salt Lake City. Fee to be announced. 28 hrs. Contact: Linda Twitchell, (801) 581-8633.

February 17-20—**26th Annual Ob/Gyn Update** (Sponsor: University of Utah). Sunday-Wednesday. Park City Holiday Inn/Yarrow. Fee to be announced. 14 hrs. Contact: Maria Vescio, (801) 581-7647.

February 20-23—**Reproductive Endocrinology and Infertility** (Sponsor: University of Utah). Wednesday-Saturday. Park City Holiday Inn/Yarrow. Fee to be announced. 14 hrs. Contact: Maria Vescio, (801) 581-7647.

February 22-26—**30th Annual Postgrad Course in Anesthesiology** (Sponsor: University of Utah). Friday-Tuesday. Salt Lake City. Fee to be announced. 16 hrs. Contact: Vicky Larsen, (801) 581-6115.

February 25-March 1—**Advances in Internal Medicine** (Sponsor: University of Utah). Monday-Friday. Snowbird. Fee to be announced. 25 hrs. Contact: Malcolm Berenson, MD, (801) 581-3581.

March 4-8—**Medical and Surgical Advances in Gastroenterology** (Sponsor: University of Utah). Monday-Friday. Snowbird. Fee to be announced. 25 hrs. Contact: Malcolm Berenson, MD, (801) 581-3581.

March 6-8—**Common Problems in Pediatrics VII** (Sponsor: University of Utah). Wednesday-Friday. Little America Hotel, Salt Lake City. Fee to be announced. 12 hrs. Contact: Wendy Ellis, (801) 363-1887 or Robert Bolte, MD, (801) 363-1221.

(Continued on Page 146)

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Charter Baywood Hospital

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Long Beach, California 90805
(213) 634-9102

Beds: 227
Psychiatric Staff: 59
Programs: Adult, Adolescent and Child Psychiatric

Other Programs: Christian Psychiatric Unit; 24 Hour Crisis Intervention Service; Psychiatric Emergency Team

For further information about Charter Baywood or admission procedures, contact:

Acting Medical Director:
Leon Marder, M.D.
Hospital Administrator: Diana Goulet

Charter Grove Hospital

2005 Kellogg Drive
Corona, California 91720
(714) 735-2910

Beds: 86
Psychiatric Staff: 15
Programs: Adult and Adolescent Psychiatric; Adult Addictive Disease.

Other Programs: Women's Program; Eating Disorders; and Christian Psychiatric

For further information about Charter Grove or admission procedures, contact:

Medical Director: William Cohen, M.D.
Hospital Administrator: Jim Fridlington

Charter Oak Hospital

1161 East Covina Blvd.
Covina, California 91724
(213) 966-1632

Beds: 74
Psychiatric Staff: 14
Programs: Adult, Adolescent and Child Psychiatric; Adult Addictive Disease

Other Programs: Premenstrual Syndrome Clinic

For further information about Charter Oak or admission procedures, contact:

President of Medical Staff:
Adib Bitar, M.D.
Hospital Administrator: Jim Sholes

Charter Pacific Hospital

4025 West 226th St.
Torrance, California 90505
(213) 373-7733

Beds: 96
Psychiatric Staff: 36
Programs: Adolescent, Child and Young Adult Psychiatric; Adult and Adolescent Addictive Disease

Other Programs: Pediatric Neuro/developmental Diagnostic Unit; Charter Clinic, in Santa Ana, offers Neuropsychological child and adolescent services.

For further information about Charter Pacific or admission procedures, contact:

Director of Adolescent Unit:
Michael J. Levine,
Hospital Administrator: Jim Hackett

CHARTER MEDICAL CORPORATION

Books Received

Books received by THE WESTERN JOURNAL OF MEDICINE *are acknowledged in this column. Selections will be made for more extensive review in the interest of readers as space permits.*

MANAGEMENT OF WILDERNESS AND ENVIRONMENTAL EMERGENCIES—Edited by Paul S. Auerbach, MD, Assistant Clinical Professor of Medicine, University of California, San Francisco, Attending Physician, Emergency Services, San Francisco General Hospital; and Edward C. Geehr, MD, Assistant Clinical Professor of Medicine, University of California, San Francisco, Medical Director of Emergency Medical Services, City and County of San Francisco. Macmillan Publishing Company, 866 Third Ave, New York, NY 10022, 1983. 656 pages, $68.00.

THE OPERATION—Gordon Thomas. Doubleday & Company, Inc, 245 Park Ave, New York, NY 10167, 1984. 192 pages, $14.95.

OPERATIVE ENDOSCOPY OF THE DIGESTIVE TRACT—Dr Giuliano Bedogni, Department of Digestive Endoscopy, Associate Chief of 2nd General Surgery Unit, St. Maria Nuova Hospital, Reggio Emilia; Prof Domenico Oselladore, Associate Clinical Professor of Gastroenterologic Surgery, University of Padua; Dr Enrico Ricci, Department of Digestive Endoscopy, Assistant of 2nd General Surgery Unit, St. Maria Nuova Hospital, Reggio Emilia; and Dr Rossana Rossoni, Assistant of 2nd Surgery Clinic, University of Padua, Italy. Ishiyaku EuroAmerica, Inc, 11559 Rock Island Court, St Louis, MO 63043. 269 pages, $80.00.

PATHOLOGY OF SKELETAL MUSCLE—Stirling Carpenter, MD, Professor, Department of Neurology and Neurosurgery, McGill University, and Chief of Neuropathology, Montreal Neurological Institute, and George Karpati, MD, FRCP(C), Professor, Department of Neurology and Neurosurgery, McGill University, and Neurologist and Director, Laboratory of Neuromuscular Research, Montreal Neurological Institute, Montreal. Churchill Livingstone, Inc, 1560 Broadway, New York, NY 10035, 1984. 740 pages, $98.00.

PREGNANCY, DIABETES AND BIRTH—A MANAGEMENT GUIDE—Dorothy Reycroft Hollingsworth, MD, Professor of Reproductive Medicine and Medicine, University of California, San Diego, School of Medicine. Williams & Wilkins, 428 E. Preston St., Baltimore, MD 21202, 1984. 159 pages, no price given.

PSYCHIATRIC EMERGENCIES— Volume 4 in Clinics in Emergency Medicine—Edited by William R. Dubin, MD, Clinical Associate Professor of Psychiatry, Department of Psychiatry and Human Behavior, and Director, Adult Services, Jefferson Medical College of Thomas Jefferson University Hospital, Philadelphia; Nancy Hande, MD, Assistant Professor of Psychiatry, University of Pennsylvania School of Medicine, and Director, Psychiatric Emergency Service, Hospital of the University of Pennsylvania, Philadelphia, and Herbert W. Nickens, MD, MA, Assistant Professor of Psychiatry, University of Pennsylvania School of Medicine, Philadelphia, and Deputy Chief, Center for the Studies of the Mental Health of the Aging, National Institute of Mental Health, Baltimore, Maryland. Churchill Livingstone, Inc, 1560 Broadway, New York, NY 10036, 1984. 262 pages, $29.00.

SOFT AND HARD TISSUE REPAIR—BIOLOGICAL AND CLINICAL ASPECTS— Volume 2 in Surgical Science Series— Edited by Thomas K. Hunt, MD, Department of Surgery, University of California, San Francisco, School of Medicine; R. Bruce Heppenstall, MD, Department of Orthopaedic Surgery, University of Pennsylvania School of Medicine, Philadelphia; Eli Pines, PhD, and David T. Rovee, PhD, Wound Care Research, Johnson & Johnson Products, Inc, New Brunswick, New Jersey. Praeger, 521 Fifth Ave, New York, NY 10175, 1984. 595 pages, $49.95.

SPEAKING THE LANGUAGE OF SIGN—THE ART AND SCIENCE OF SIGNING—Jerome D. Schein, PhD, Director, Deafness Research and Training Center, New York University. Doubleday & Company, Inc, 245 Park Ave, New York, NY 10167, 1984. 183 pages, $9.95 (paperback).

TECHNOLOGY OF NUCLEAR MAGNETIC RESONANCE—Edited by Peter D. Esser, PhD, Department of Nuclear Medicine, College of Physicians and Surgeons, New York, and R. Eugene Johnston, PhD, University of North Carolina, Chapel Hill. The Society of Nuclear Medicine, Inc, 475 Park Ave South, New York, NY 10016, 1984. 257 pages, no price given (paperback).

UNDERSTAND YOUR BACKACHE— A GUIDE TO PREVENTION, TREATMENT, AND RELIEF—Rene Cailliet, MD, Director of Rehabilitation Services, Santa Monica Hospital Medical Center, Santa Monica, California, and Professor and Chairman (Retired), Department of Rehabilitative Medicine, USC School of Medicine, Los Angeles. F. A. Davis, Co, 1915 Arch St, Philadelphia, PA 19103, 1984. 181 pages, $10.95 (paperback).

BASIC & CLINICAL IMMUNOLOGY—5th Edition—Edited by Daniel P. Stites, MD, Professor of Medicine and Laboratory Medicine and Director, Immunology Laboratory, University of California, San Francisco; John D. Stobo, MD, Professor of Medicine and Head, Section of Rheumatology and Clinical Immunology, Moffitt Hospital and Howard Hughes Medical Institute, University of California, San Francisco; H. Hugh Fudenberg, MD, Professor of Medicine and Chairman of Basic and Clinical Immunology and Microbiology, Medical University of South Carolina, Charleston, and J. Vivian Wells, MD, FRACP, FRCPA, Senior Staff Speicalist in Clinical Immunology, Kolling Institute of Medical Research, Royal North Shore Hospital, Sydney, Australia. Lange Medical Publications, Drawer L, Los Altos, CA 94022, 1984. 776 pages, $25.00 (softbound).

CLINICAL BIOCHEMISTRY OF THE ELDERLY—Edited by Malcolm Hodkinson, MA, DM, FRCP, Professor of Geriatric Medicine, Hammersmith Hospital, London, United Kingdom. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1984. 326 pages, $44.00.

COMPUTERS IN RADIOLOGY—George B. Greenfield, MD, Professor of Diagnostic Radiology, Rush Medical College; Chairman, Department of Radiology, Mount Sinai Hospital Medical Center; Consultant Radiologist, Cook County Hospital, Chicago, and Lincoln B. Hubbard, PhD, Visiting Associate Professor, Medical Physics, Rush University; Chief, Radiological Physicist, Mount Sinai Hospital Medical Center; Chief of Radiation Physics and Medical Dosimetry, Cook County Hospital, Chicago. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1984. 183 pages, $30.00.

CONTROVERSIES IN GASTROENTEROLOGY—Edited by Gary Gitnick, MD, Professor, Department of Medicine, UCLA School of Medicine, Los Angeles. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1984. 276 pages, $30.00.

CONTINUING MEDICAL EDUCATION

(Continued from Page 143)

March 12-22—**Transport Workshop: Neonatal-Maternal-Administration** (Sponsor: University of Utah). Tuesday-Friday. Salt Lake City. Fee to be announced. 69½ hrs. Contact: Anne Shanahan, (801) 581-2730.

March 18-22—**5th Annual Nutrition in Contemporary Medicine Symposium** (Sponsor: University of Utah). Monday-Friday. Park City. Fee to be announced. 29 hrs. Contact: M. Rita Thomas, MD, (801) 581-3581.

March 21-23—**Practical Neurology for Clinicians** (Sponsor: University of Utah). Thursday-Saturday. Sheraton Hotel, Salt Lake City. Fee to be announced. 18 hrs. Contact: Richard Baringer, MD, (801) 581-8664.

WASHINGTON

This listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121; or phone (206) 623-4801.

Brochures and Registration Forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

January 15—**General Topics in Hematology.** Seattle. Tuesday. Ballard Hospital. Contact: U/W.

January 18—**Timely Theophyllic Therapy.** Seattle. Friday. Riverton Hospital. Contact: U/W.

January 22—**Diagnosis and Management of Allergic Diseases.** Auburn. Tuesday. Auburn General Hospital. Contact: U/W.

January 23-25—(MONTANA) **Internal Medicine Review.** Great Falls, Billings, Missoula. Wednesday-Friday. Contact: U/W.

January 24-26—**Annual President's Meeting—**

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

CME PIERCE COUNTY—Contact: Mrs Maxine Bailey, Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 223-6898.

Modern Ophthalmic Technology. Washington State Academy of Ophthalmology at Seattle. Thursday-Saturday. Westin. Contact: Patti Smith, WSAO, 2033 Sixth Ave, #900, Seattle 98121. (206) 623-4801.

January 25—**Foot Problems in Kids and Adolescents.** Seattle. Friday. Riverton Hospital. Contact: U/W.

January 30—**Controversies in Medicine Circuit.** Vancouver. Wednesday. Contact: U/W.

January 31—**Controversies in Medicine Circuit.** Olympia. Thursday. Contact: U/W.

January 31-February 1—**Updates in Cardiology.** Seattle. Thursday-Friday. Westin. Contact: U/W.

February 1—**Life, Death and the "Cost" of Care.** Seattle. Friday. Riverton Hospital. Contact: U/W.

February 1-2—**Medical and Surgical Update for Psychiatrists.** Seattle. Friday-Saturday. Contact: VMMC.

February 8—**Drug Therapy in the Elderly.** Seattle. Friday. Riverton Hospital. Contact: U/W.

February 15—**Acute Abdominal Trauma.** Seattle. Friday. Riverton Hospital. Contact: U/W.

February 16—**Interventional Radiology to Abdomen.** Seattle. Saturday. U/W South Campus Center. Contact: U/W.

February 16-23—(IDAHO) **Internal Medicine.** Sun Valley. Saturday-Saturday. Elkhorn Resort. Contact: U/W.

February 19—**Total and Home Parenteral Nutrition.** Seattle. Tuesday. Ballard Hospital. Contact: U/W.

February 20-22—(MONTANA) **Internal Medicine Review.** Great Falls, Billings, Missoula. Wednesday-Friday. Contact: U/W.

February 22—**Olympic Experience With Lung Functions.** Seattle. Friday. Riverton Hospital. Contact: U/W.

February 22-23—**Hemodynamic Monitoring Workshop.** Seattle. Friday-Saturday. Contact: VMMC.

February 23-March 2—(IDAHO) **Office Orthopaedics.** Sun Valley. Saturday- Saturday. Elkhorn Resort. Contact: U/W.

February 26—**Management of Pain.** Auburn. Tuesday. Auburn General Hospital. Contact: U/W.

March 1—**Thrombolytic Therapy of MI.** Seattle. Friday. Riverton Hospital. Contact: U/W.

March 2-9—(HAWAII) **Medicine in China.** Kauai. Saturday-Saturday. Royal Waikola. Contact: U/W.

March 2-9—(IDAHO) **Electromyography.** Sun Valley. Saturday-Saturday. Elkhorn Resort. Contact: U/W.

March 8—**Riverton Hospital Lectures.** Seattle. Friday. Riverton Hospital. Contact: U/W.

March 9-16—(HAWAII) **Imaging Solutions for the 80s.** Kona. Saturday-Saturday. Royal Waikoloa. Contact: U/W.

March 15—**Soft Tissue Surgery.** Seattle. Friday. Contact: VMMC.

March 15—**Riverton Hospital Lectures.** Seattle. Friday. Riverton Hospital. Contact: U/W.

March 16-23—(HAWAII) **Drug Therapy.** Maui. Saturday-Saturday. Royal Lahaina. Contact: U/W.

March 19—**Epilepsy.** Seattle. Tuesday. Ballard Hospital. Contact: U/W.

March 21-22—**Advances in Internal Medicine.** Seattle. Thursday-Friday. U/W HUB. Contact: U/W.

March 22—**Medicine in Mainland China.** Seattle. Friday. Riverton Hospital. Contact: U/W.

March 23—**Magnetic Resonance Imaging.** Seattle. Saturday. U/W South Campus Center. Contact: U/W.

March 23-30—(HAWAII) **Vascular Surgery.** Maui. Saturday-Saturday. Royal Lahaina. Contact: U/W.

March 26—**Alzheimer's Disease.** Auburn. Tuesday. Auburn General Hospital. Contact: U/W.

March 29—**Convulsing and Sloppy Kids.** Seattle. Friday. Riverton Hospital. Contact: U/W.

March 30-April 6—(HAWAII) **Neurology Update.** Maui. Saturday-Saturday. Royal Lahaina. Contact: U/W.

April 5—**Riverton Hospital Lectures.** Seattle. Friday. Riverton Hospital. Contact: U/W.

April 11-12—**DRG.** Seattle. Thursday-Friday. Westin. Contact: U/W.

April 12—**Riverton Hospital Lectures.** Seattle. Friday. Riverton Hospital. Contact: U/W.

April 13—**Handicapped Infant.** Seattle. Saturday. U/W Health Sciences. Contact: U/W.

April 13—**Mason Clinic Day.** Seattle. Saturday. Contact: VMMC.

April 16—**Alzheimer's Disease.** Seattle. Tuesday. Ballard Hospital. Contact: U/W.

April 17-19—(MONTANA) **Internal Medicine Review.** Great Falls, Billings, Missoula. Wednesday-Friday. Contact: U/W.

April 18-20—**Death Investigation.** Seattle. Thursday-Saturday. Westin. Contact: U/W.

April 19—**Riverton Hospital Lectures.** Seattle. Friday. Riverton Hospital. Contact: U/W.

April 22-May 3—**Rehab Medicine Review.** Seattle. 12 days. Seattle Sheraton. Contact: U/W.

April 23—**Sexually Transmitted Diseases.** Auburn. Tuesday. Auburn General Hospital. Contact: U/W.

April 26—**Riverton Hospital Lectures.** Seattle. Friday. Riverton Hospital. Contact: U/W.

April 26-27—**Sexual Assault.** Seattle. Friday-Saturday. Westin Hotel. Contact: U/W.

May 3—**Riverton Hospital Lectures.** Seattle. Friday. Riverton Hospital. Contact: U/W.

May 3-4—**Pharmacology Update.** Seattle. Friday-Saturday. Contact: VMMC.

May 9-10—**Issues in General Pediatrics.** Seattle. Thursday-Friday. Children's Orthopedic Hospital. Contact: U/W.

May 10—**Riverton Hospital Lectures.** Seattle. Friday. Riverton Hospital. Contact: U/W.

May 17—**Riverton Hospital Lectures.** Seattle. Friday. Riverton Hospital. Contact: U/W.

May 18—**Microcomputers in Rehab Medicine.** Seattle. Saturday. Contact: U/W.

May 21—**Using Pulmonary Function Tests.** Seattle. Tuesday. Ballard Hospital. Contact: U/W.

May 22-24—(MONTANA) **Internal Medicine Review.** Great Falls, Billings, Missoula. Wednesday-Friday. Contact: U/W.

May 28—**Travel and Illness.** Auburn. Tuesday. Auburn General Hospital. Contact: U/W.

May 30-31—**Controversies in Cardiovascular Issues.** Seattle. Thursday-Friday. Contact: U/W.

May 30-31—**Mental Health Policy Forum.** Seattle. Thursday-Friday. Westin. Contact: U/W.

May 31—**Riverton Hospital Lectures.** Seattle. Friday. Riverton Hospital. Contact: U/W.

June 6-7—**Behavioral Medicine.** Seattle. Thursday-Friday. Westin. Contact: U/W.

June 6-8—**Medical Emergencies.** Seattle. Thursday-Saturday. Contact: VMMC.

June 7—**Riverton Hospital Lectures.** Seattle. Friday. Riverton Hospital. Contact: U/W.

June 13-14—**Ischemic Heart Disease.** Seattle. Thursday-Friday. Westin. Contact: U/W.

June 13-14—**Advances in Internal Medicine.** Seattle. Thursday-Friday. U/W HUB. Contact: U/W.

June 14—**Riverton Hospital Lectures.** Seattle. Friday. Riverton Hospital. Contact: U/W.

June 15—**Contemporary Thoracic Imaging.** Seattle. Saturday. U/W South Campus Center. Contact: U/W.

June 18—**Small Computers in Medicine.** Seattle. Tuesday. Ballard Hospital. Contact: U/W.

June 19-20—**Financial Planning for Physicians.** Victoria, BC. Wednesday-Friday. Empress Hotel. Contact: U/W.

June 21—**Riverton Hospital Lectures.** Seattle. Friday. Riverton Hospital. Contact: U/W.

June 21-22—**Nutrition of Hospitalized Patient.** Vancouver, BC. Saturday-Sunday. Contact: U/W.

June 24-28—(OREGON) **Prevention of Cardiovascular Disease.** Sunriver. Tuesday-Friday. Sunriver Resort. Contact: U/W.

June 25—**What's New in Antibiotics.** Auburn. Tuesday. Auburn General Hospital. Contact: U/W.

June 28—**Riverton Hospital Lectures.** Seattle. Friday. Riverton Hospital. Contact: U/W.

July 8-10—**Exercising Women.** Seattle. Monday-Wednesday. Westin. Contact: U/W.

WYOMING

January 25-26—**20th Annual Wyoming Medical Society Winter Seminar—Coronary Artery Disease Update—1985.** Holiday Inn, Cheyenne. Friday-Saturday. 10 hrs. Cat. 1. $50, WMS members; $100, nonmembers. Contact: Wyoming Medical Society, PO Box 4009, Cheyenne 82003. (307) 635-2424. ◆

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AMWA
AMERICAN MEDICAL WRITERS ASSOCIATION

WESTERN STATE MEDICAL ASSOCIATIONS' MEETINGS

Alaska State Medical Association—4107 Laurel St., Anchorage 99504. (907) 562-2662. Annual Meeting: June 8-11, 1985, Haines.

Arizona Medical Association, Inc.—810 W. Bethany Home Rd., Phoenix 85013. (602) 246-8901. Annual Meeting: April 26-27, 1985, The Cottonwoods, Scottsdale.

California Medical Association—44 Gough St., San Francisco 94103. (415) 863-5522. Annual Meeting: March 8-13, 1985, Town and County, San Diego.

Colorado Medical Society—6825 E. Tennessee, Bldg. 2, Suite 500, Denver 80224. (303) 321-8590. Annual Meeting: September 11-14, 1985, Broadmoor, Colorado Springs.

Hawaii Medical Association—320 Ward Ave., Suite 200, Honolulu 96814. (808) 536-7702. Annual Meeting: 1985—date and place to be announced.

Idaho Medical Association—407 W. Bannock St., PO Box 2668, Boise 83701. (208) 344-7888. Annual Meeting: July 24-27, 1985, Sun Valley.

Montana Medical Association—2012 11th Ave., Suite 12, Helena 59601. (406) 443-4000. Annual Meeting: October 3-5, 1985, Outlaw Inn, Kalispell.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: May 9-12, 1985, Hyatt, Lake Tahoe.

New Mexico Medical Society—303 San Mateo NE, Suite 204, Albuquerque 87108. (505) 266-7868. Annual Meeting: May 1-3, 1985, Marriott, Albuquerque.

Oregon Medical Association—5210 S.W. Corbett Ave., Portland 97201. (503) 226-1555. Annual Meeting: (House of Delegates only): April 26-28, 1985, Ashland Hills Inn, Ashland.

Utah State Medical Association—540 East Fifth South, Salt Lake City 84102. (801) 355-7477. Annual Meeting: September 26-27, 1985. Hotel Utah, Salt Lake City.

Washington State Medical Association—900 United Airlines Bldg., 2033 6th Ave., Seattle 98121. (206) 623-4801. Annual Meeting: September 19-22, 1985, Jantzen Beach.

Wyoming Medical Society—P.O. Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. Annual Meeting: June 23-26, 1985, Jackson Lake Lodge, Moran.

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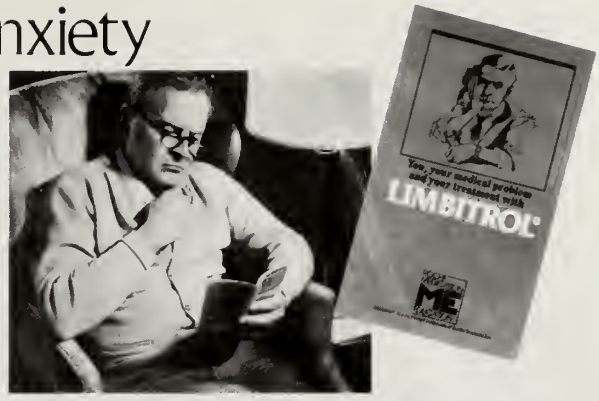

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Warnings: Use with great care in patients with history of urinary retention or angle-closure glaucoma. Severe constipation may occur in patients taking tricyclic antidepressants and anticholinergic-type drugs. Closely supervise cardiovascular patients. (Arrhythmias, sinus tachycardia and prolongation of conduction time reported with use of tricyclic antidepressants, especially high doses.) Myocardial infarction and stroke reported with use of this class of drugs.) Caution patients about possible combined effects with alcohol and other CNS depressants and against hazardous occupations requiring complete mental alertness (e.g., operating machinery, driving).

***Usage in Pregnancy:* Use of minor tranquilizers during the first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Since physical and psychological dependence to chlordiazepoxide have been reported rarely, use caution in administering Limbitrol to addiction-prone individuals or those who might increase dosage. Withdrawal symptoms following discontinuation of either component alone have been reported (nausea, headache and malaise for amitriptyline; symptoms [including convulsions] similar to those of barbiturate withdrawal for chlordiazepoxide).
Precautions: Use with caution in patients with a history of seizures, in hyperthyroid patients or those on thyroid medication, and in patients with impaired renal or hepatic function. Because of the possibility of suicide in depressed patients, do not permit easy access to large quantities in these patients. Periodic liver function tests and blood counts are recommended during prolonged treatment. Amitriptyline component may block action of guanethidine or similar antihypertensives. Concomitant use with other psychotropic drugs has not been evaluated; sedative effects may be additive. Discontinue several days before surgery. Limit concomitant administration of ECT to essential treatment. See Warnings for precautions about pregnancy. Limbitrol should not be taken during the nursing period. Not recommended in children under 12. In the elderly and debilitated, limit to smallest effective dosage to preclude ataxia, oversedation, confusion or anticholinergic effects.
Adverse Reactions: Most frequently reported are those associated with either component alone: drowsiness, dry mouth, constipation, blurred vision, dizziness and bloating. Less frequently occurring reactions include vivid dreams, impotence, tremor, confusion and nasal congestion. Many depressive symptoms including anorexia, fatigue, weakness, restlessness and lethargy have been reported as side effects of both Limbitrol and amitriptyline. Granulocytopenia, jaundice and hepatic dysfunction have been observed rarely.
The following list includes adverse reactions not reported with Limbitrol but requiring consideration because they have been reported with one or both components or closely related drugs:
Cardiovascular: Hypotension, hypertension, tachycardia, palpitations, myocardial infarction, arrhythmias, heart block, stroke.
Psychiatric: Euphoria, apprehension, poor concentration, delusions, hallucinations, hypomania and increased or decreased libido.
Neurologic: Incoordination, ataxia, numbness, tingling and paresthesias of the extremities, extrapyramidal symptoms, syncope, changes in EEG patterns.
Anticholinergic: Disturbance of accommodation, paralytic ileus, urinary retention, dilatation of urinary tract.
Allergic: Skin rash, urticaria, photosensitization, edema of face and tongue, pruritus.
Hematologic: Bone marrow depression including agranulocytosis, eosinophilia, purpura, thrombocytopenia.
Gastrointestinal: Nausea, epigastric distress, vomiting, anorexia, stomatitis, peculiar taste, diarrhea, black tongue.
Endocrine: Testicular swelling and gynecomastia in the male, breast enlargement, galactorrhea and minor menstrual irregularities in the female, elevation and lowering of blood sugar levels, and syndrome of inappropriate ADH (antidiuretic hormone) secretion.
Other: Headache, weight gain or loss, increased perspiration, urinary frequency, mydriasis, jaundice, alopecia, parotid swelling.
Overdosage: Immediately hospitalize patient suspected of having taken an overdose. Treatment is symptomatic and supportive. I.V. administration of 1 to 3 mg physostigmine salicylate has been reported to reverse the symptoms of amitriptyline poisoning. See complete product information for manifestation and treatment.
Dosage: Individualize according to symptom severity and patient response. Reduce to smallest effective dosage when satisfactory response is obtained. Larger portion of daily dose may be taken at bedtime. Single h.s. dose may suffice for some patients. Lower dosages are recommended for the elderly.
Limbitrol 10-25, initial dosage of three or four tablets daily in divided doses, increased up to six tablets or decreased to two tablets daily as required. Limbitrol 5-12.5, initial dosage of three or four tablets daily in divided doses, for patients who do not tolerate higher doses.
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References: 1. Kales J *et al: Clin Pharmacol Ther 12*:691-697, Jul-Aug 1971. **2.** Kales A *et al: Clin Pharmacol Ther 18*:356-363, Sep 1975. **3.** Kales A *et al: Clin Pharmacol Ther 19*:576-583, May 1976. **4.** Kales A *et al: Clin Pharmacol Ther 32*:781-788, Dec 1982. **5.** Frost JD Jr, DeLucchi MR: *J Am Geriatr Soc 27*:541-546, Dec 1979. 6. Kales A, Kales JD: *J Clin Pharmacol* 3:140-150, Apr 1983. **7.** Greenblatt DJ, Allen MD, Shader RI: *Clin Pharmacol Ther 21*:355-361, Mar 1977. **8.** Zimmerman AM: *Curr Ther Res 13*:18-22, Jan 1971. **9.** Amrein R *et al: Drugs Exp Clin Res* 9(1):85-99, 1983. **10.** Monti JM. *Methods Find Exp Clin Pharmacol 3*:303-326, May 1981. **11.** Greenblatt DJ *et al: Sleep 5*(Suppl 1):S18-S27, 1982. **12.** Kales A *et al: Pharmacology 26*:121-137, 1983.

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Indications: Effective in all types of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings and/or early morning awakening, in patients with recurring insomnia or poor sleeping habits; in acute or chronic medical situations requiring restful sleep. Objective sleep laboratory data have shown effectiveness for at least 28 consecutive nights of administration. Since insomnia is often transient and intermittent, prolonged administration is generally not necessary or recommended. Repeated therapy should only be undertaken with appropriate patient evaluation.

Contraindications: Known hypersensitivity to flurazepam HCl; pregnancy. Benzodiazepines may cause fetal damage when administered during pregnancy. Several studies suggest an increased risk of congenital malformations associated with benzodiazepine use during the first trimester. Warn patients of the potential risks to the fetus should the possibility of becoming pregnant exist while receiving flurazepam. Instruct patient to discontinue drug prior to becoming pregnant. Consider the possibility of pregnancy prior to instituting therapy.

Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. An additive effect may occur if alcohol is consumed the day following use for nighttime sedation. This potential may exist for several days following discontinuation. Caution against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). Potential impairment of performance of such activities may occur the day following ingestion. Not recommended for use in persons under 15 years of age. Though physical and psychological dependence have not been reported on recommended doses, abrupt discontinuation should be avoided with gradual tapering of dosage for those patients on medication for a prolonged period of time. Use caution in administering to addiction-prone individuals or those who might increase dosage.

Precautions: In elderly and debilitated patients, it is recommended that the dosage be limited to 15 mg to reduce risk of oversedation, dizziness, confusion and/or ataxia. Consider potential additive effects with other hypnotics or CNS depressants. Employ usual precautions in severely depressed patients, or in those with latent depression or suicidal tendencies, or in those with impaired renal or hepatic function.

Adverse Reactions: Dizziness, drowsiness, lightheadedness, staggering, ataxia and falling have occurred, particularly in elderly or debilitated patients. Severe sedation, lethargy, disorientation and coma, probably indicative of drug intolerance or overdosage, have been reported. Also reported: headache, heartburn, upset stomach, nausea, vomiting, diarrhea, constipation, GI pain, nervousness, talkativeness, apprehension, irritability, weakness, palpitations, chest pains, body and joint pains and GU complaints. There have also been rare occurrences of leukopenia, granulocytopenia, sweating, flushes, difficulty in focusing, blurred vision, burning eyes, faintness, hypotension, shortness of breath, pruritus, skin rash, dry mouth, bitter taste, excessive salivation, anorexia, euphoria, depression, slurred speech, confusion, restlessness, hallucinations, and elevated SGOT, SGPT, total and direct bilirubins, and alkaline phosphatase; and paradoxical reactions, *e.g.*, excitement, stimulation and hyperactivity.

Dosage: Individualize for maximum beneficial effect. *Adults:* 30 mg usual dosage; 15 mg may suffice in some patients. *Elderly or debilitated patients:* 15 mg recommended initially until response is determined.

Supplied: Capsules containing 15 mg or 30 mg flurazepam HCl.

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SORBITRATE®
(ISOSORBIDE DINITRATE)

Please consult full prescribing information before use. A summary follows:

INDICATIONS AND USAGE: SORBITRATE (isosorbide dinitrate) is indicated for the treatment and prevention of angina pectoris. All dosage forms of isosorbide dinitrate may be used prophylactically to decrease frequency and severity of anginal attacks and can be expected to decrease the need for sublingual nitroglycerin.

The sublingual and chewable forms of the drug are indicated for acute prophylaxis of angina pectoris when taken a few minutes before situations likely to provoke anginal attacks. Because of a slower onset of effect, the oral forms of isosorbide dinitrate are not indicated for acute prophylaxis.

CONTRAINDICATIONS: SORBITRATE is contraindicated in patients who have shown purported hypersensitivity or idiosyncrasy to it or other nitrates or nitrites. Epinephrine and related compounds are ineffective in reversing the severe hypotensive events associated with overdose and are contraindicated in this situation.

WARNINGS: The benefits of SORBITRATE during the early days of an acute myocardial infarction have not been established. If one elects to use organic nitrates in early infarction, hemodynamic monitoring and frequent clinical assessment should be used because of the potential deleterious effects of hypotension.

PRECAUTIONS: General: Severe hypotensive response, particularly with upright posture, may occur with even small doses of SORBITRATE. The drug should therefore be used with caution in subjects who may have blood volume depletion from diuretic therapy or in subjects who have low systolic blood pressure (eg, below 90 mmHg). Paradoxical bradycardia and increased angina pectoris may accompany nitrate-induced hypotension. Nitrate therapy may aggravate the angina caused by hypertrophic cardiomyopathy.

Marked symptomatic orthostatic hypotension has been reported when calcium channel blockers and organic nitrates were used in combination. Dose adjustment of either class of agents may be necessary.

Tolerance to this drug and cross-tolerance to other nitrates and nitrites may occur. Tolerance to the vascular and antianginal effects of isosorbide dinitrate or nitroglycerin has been demonstrated in clinical trials, experience through occupational exposure, and in isolated tissue experiments in the laboratory. The importance of tolerance to the appropriate use of isosorbide dinitrate in the management of patients with angina pectoris has not been determined. However, one clinical trial using treadmill exercise tolerance (as an end point) found an 8-hour duration of action of oral isosorbide dinitrate following the first dose (after a 2-week placebo washout) and only a 2-hour duration of effect of the same dose after 1 week of repetitive dosing at conventional dosing intervals. On the other hand, several trials have been able to differentiate isosorbide dinitrate from placebo after 4 weeks of therapy and, in open trials, an effect seems detectable for as long as several months.

Tolerance clearly occurs in industrial workers continuously exposed to nitroglycerin. Moreover, physical dependence also occurs since chest pain, acute myocardial infarction, and even sudden death have occurred during temporary withdrawal of nitroglycerin from the workers. In clinical trials in angina patients, there are reports of anginal attacks being more easily provoked and of rebound in the hemodynamic effects soon after nitrate withdrawal. The relative importance of these observations to the routine, clinical use of isosorbide dinitrate is not known. However, it seems prudent to gradually withdraw patients from isosorbide dinitrate when the therapy is being terminated, rather than stopping the drug abruptly.

Information for Patients: Headache may occur during initial therapy with SORBITRATE. Headache is usually relieved by the use of standard headache remedies or by lowering the dose and tends to disappear after the first week or two of use.

Drug Interactions: Alcohol may enhance any marked sensitivity to the hypotensive effect of nitrates.

Isosorbide dinitrate acts directly on vascular smooth muscle; therefore, any other agent that depends on vascular smooth muscle as the final common path can be expected to have decreased or increased effect depending on the agent.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No long-term studies in animals have been performed to evaluate the carcinogenic potential of this drug. A modified two-litter reproduction study in rats fed isosorbide dinitrate at 25 or 100 mg/kg/day did not reveal any effects on fertility or gestation or any remarkable gross pathology in any parent or offspring fed isosorbide dinitrate as compared with rats fed a basal-controlled diet.

Pregnancy Category C: Isosorbide dinitrate has been shown to cause a dose-related increase in embryotoxicity (increase in mummified pups) in rabbits at oral doses 35 and 150 times the maximum recommended human daily dose. There are no adequate and well-controlled studies in pregnant women. SORBITRATE should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when SORBITRATE is administered to a nursing woman.

Pediatric Use: The safety and effectiveness of SORBITRATE in children has not been established.

ADVERSE REACTIONS: Adverse reactions, particularly headache and hypotension, are dose-related. In clinical trials at various doses, the following have been observed.

Headache is the most common (reported incidence varies widely, apparently being dose-related, with an average occurrence of about 25%) adverse reaction and may be severe and persistent. Cutaneous vasodilation with flushing may occur. Transient episodes of dizziness and weakness, as well as other signs of cerebral ischemia associated with postural hypotension, may occasionally develop (the incidence of reported symptomatic hypotension ranges from 2% to 36%). An occasional individual will exhibit marked sensitivity to the hypotensive effects of nitrates and severe responses (nausea, vomiting, weakness, restlessness, pallor, perspiration, and collapse) may occur even with the usual therapeutic dose. Drug rash and/or exfoliative dermatitis may occasionally occur. Nausea and vomiting appear to be uncommon. Case reports of clinically significant methemoglobinemia are rare at conventional doses of organic nitrates. The formation of methemoglobin is dose-related and, in the case of genetic abnormalities of hemoglobin that favor methemoglobin formation, even conventional doses of organic nitrate could produce harmful concentrations of methemoglobin.

DOSAGE AND ADMINISTRATION: For the treatment of angina pectoris, the usual starting dose for sublingual SORBITRATE is 2.5 to 5 mg; for chewable tablets, 5 mg; for oral (swallowed) tablets, 5 to 20 mg; and for controlled-release forms, 40 mg.

SORBITRATE should be titrated upward until angina is relieved or side effects limit the dose. In ambulatory patients, the magnitude of the incremental dose increase should be guided by measurements of standing blood pressure.

The initial dosage of sublingual or chewable SORBITRATE for prophylactic therapy in angina pectoris patients is generally 5 or 10 mg every 2 to 3 hours. Adequate controlled clinical studies demonstrating the effectiveness of chronic maintenance therapy with these dosage forms have not been reported.

SORBITRATE in oral doses of 10 to 40 mg given every 6 hours or in oral controlled-release doses of 40 to 80 mg given every 8 to 12 hours is generally recommended. The extent to which development of tolerance should modify the dosage program has not been defined. *The oral controlled-release forms of isosorbide dinitrate should not be chewed.*

DOSAGE FORMS AVAILABLE: Sublingual Tablets (2.5, 5, 10 mg), Chewable Tablets (5, 10 mg), Oral Tablets (5, 10, 20, 30, 40 mg), Sustained Action Tablets (40 mg).

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See previous page for brief summary of prescribing information.

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Chief Discussant: CHARLES A. SIMONTON, MD
A discussion selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco, School of Medicine. Taken from a transcription, it was prepared by Drs Homer A. Boushey, Associate Professor of Medicine, and David G. Warnock, Associate Professor of Medicine, under the direction of Dr Lloyd H. Smith, Jr, Professor of Medicine and Chairman of the Department of Medicine.

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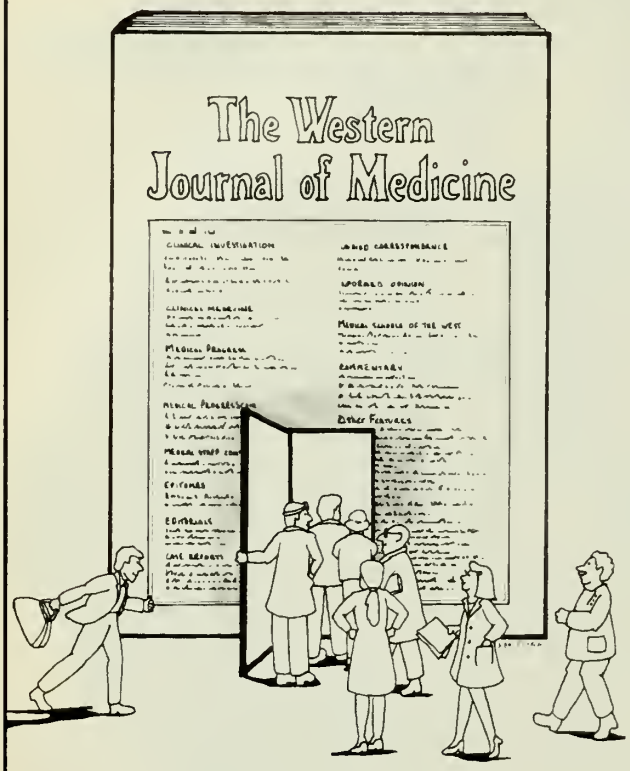

Inside Information.

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(Continued from adjacent page)

Nursing Mothers: Captopril is secreted in hu man milk. Exercise caution when administerin captopril to a nursing woman, and, in general nursing should be interrupted.

Pediatric Use: Safety and effectiveness in chil dren have not been established although there i limited experience with use of captopril in chil dren from 2 months to 15 years of age. Dosage on a weight basis, was comparable to that use in adults. Captopril should be used in childre only if other measures for controlling blood pres sure have not been effective.

ADVERSE REACTIONS: Reported inci dences are based on clinical trials involving abou 4000 patients.

Renal—One to 2 of 100 patients develope proteinuria (see WARNINGS). Renal insuffi ciency, renal failure, polyuria, oliguria, and uri nary frequency in 1 to 2 of 1000 patients.

Hematologic—Neutropenia/agranulocytosis oc curred in about 0.3% of captopril treated patient (see WARNINGS). Two of these patients devel oped sepsis and died.

Dermatologic—Rash (usually mild, maculopap ular, rarely urticarial), often with pruritus an sometimes with fever and eosinophilia, in abou 10 of 100 patients, usually during the 1st 4 week of therapy. Pruritus, without rash, in about 2 o 100 patients. A reversible associated pemphigoid like lesion, and photosensitivity have also bee reported. Angioedema of the face, mucous mem branes of the mouth, or of the extremities in abou 1 of 100 patients—reversible on discontinuanc of captopril therapy. One case of laryngeal edem reported. Flushing or pallor in 2 to 5 of 100 patients.

Cardiovascular—Hypotension in about 2 of 10 patients. See WARNINGS (Hypotension) an PRECAUTIONS (Drug Interactions) for dis cussion of hypotension on initiation of captopri therapy. Tachycardia, chest pain, and palpita tions each in about 1 of 100 patients. Angin pectoris, myocardial infarction, Raynaud's syn drome, and congestive heart failure each in 2 t 3 of 1000 patients.

Dysgeusia—About 7 of 100 patients develope a diminution or loss of taste perception; tast impairment is reversible and usually self-limite even with continued drug use (2 to 3 months) Gastric irritation, abdominal pain, nausea, vom iting, diarrhea, anorexia, constipation, aphthou ulcers, peptic ulcer, dizziness, headache, malaise fatigue, insomnia, dry mouth, dyspnea, and par esthesias reported in about 0.5 to 2% of patient but did not appear at increased frequency com pared to placebo or other treatments used i controlled trials.

Altered Laboratory Findings: Elevations o liver enzymes in a few patients although no causa relationship has been established. Rarely chole static jaundice and hepatocellular injury wit secondary cholestasis have been reported. A transient elevation of BUN and serum creatinin may occur, especially in volume-depleted o renovascular hypertensive patients. In instance of rapid reduction of longstanding or severel elevated blood pressure, the glomerular filtratio rate may decrease transiently, also resulting i transient rises in serum creatinine and BUN Small increases in serum potassium concentratio frequently occur, especially in patients with rena impairment (see PRECAUTIONS).

OVERDOSAGE: Primary concern in correc tion of hypotension. Volume expansion with a I.V. infusion of normal saline is the treatment o choice for restoration of blood pressure. Captopri may be removed from the general circulation b hemodialysis.

DOSAGE AND ADMINISTRATION: CAP OTEN should be taken one hour before meals Dosage must be individualized; see DOSAGE AND ADMINISTRATION section of package insert for detailed information regarding dosage in hypertension and in heart failure. Because CAPOTEN (captopril) is excreted primarily b the kidneys, dosage adjustments are recom mended for patients with impaired renal function. **Consult package insert before prescribing CAPOTEN (captopril).**

HOW SUPPLIED: Available in tablets of 25, 50, and 100 mg in bottles of 100, and in UNI-MATIC® unit-dose packs of 100 tablets.

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ACE INHIBITOR

Capoten®
(captopril tablets)

recautionary Guidelines

APOTEN has been associated with
ne development of neutropenia/
granulocytosis (0.3% of 4,000
atients) or proteinuria (1.2% of
,000 patients).† These serious side
ffects are more likely to occur in
atients with predisposing condi-
ons, such as renal impairment or
utoimmune disease, or in patients
eceiving therapy known to sup-
ress the autoimmune response.

he following precautionary guide-
nes are recommended for all
atients receiving CAPOTEN:

☐ Obtain urinary protein level
stimates prior to initiating therapy,
t monthly intervals for the first
ine months of treatment, and
eriodically thereafter.

☐ Obtain WBC counts at the initia-
ion of therapy, at two-week inter-
als for the first three months
f treatment, and periodically
hereafter.

☐ Carefully review the WARN-
NGS and ADVERSE REACTIONS
ections in the complete prescribing
nformation, with particular atten-
ion to the patient at increased risk.

☐ The most frequently occurring
dverse reactions are skin rash and
aste alteration; both effects are
enerally mild, reversible, or self-
imited.

Angiotensin Converting Enzyme

Please see the following brief sum-
nary of prescribing information
or INDICATIONS AND USAGE,
WARNINGS, and ADVERSE
REACTIONS.

Reference: 1. Market Measures Inc.: Treatment of Hypertension V, February 1983.

CAPOTEN® TABLETS
Captopril Tablets

INDICATIONS: Hypertension—Because serious adverse effects have been reported (see WARNINGS), CAPOTEN is indicated for treatment of hypertensive patients who on multidrug regimens have either failed to respond satisfactorily or developed unacceptable side effects.

Heart Failure: CAPOTEN (captopril) is indicated in patients with heart failure who have not responded adequately to or cannot be controlled by conventional diuretic and digitalis therapy. CAPOTEN is to be used with diuretics and digitalis.

WARNINGS: Proteinuria—Total urinary proteins >1 g/day were seen in 1.2% of patients on captopril; the nephrotic syndrome occurred in about ¼th of these cases. About 60% of affected patients had evidence of prior renal disease; the remainder had no known renal dysfunction. In most cases, proteinuria subsided or cleared within 6 months whether or not captopril was continued. The BUN and creatinine were seldom altered in proteinuric patients.

Membranous glomerulopathy was found in nearly all the proteinuric patients on captopril who were biopsied and may be drug related. Most cases of proteinuria occurred by the 8th month of therapy. Patients should have urinary protein estimates (dip-stick on 1st morning urine, or quantitative 24-hr urine—the latter provides greater precision when proteinuria is persistent and/or at low levels) before therapy, at approx. monthly intervals for the 1st 9 months of therapy, and periodically thereafter. For patients who develop proteinuria >1 g/day, or increasing proteinuria, the benefits and risks of continuing captopril should be evaluated.

Neutropenia/Agranulocytosis—Neutropenia (<300/mm³) associated with myeloid hypoplasia (probably drug related) occurred in about 0.3% of captopril treated patients. About half of the neutropenic patients developed systemic or oral cavity infections or other features of agranulocytosis. Most of the neutropenic patients had severe hypertension and renal function impairment; about half had systemic lupus erythematosus (SLE), or another autoimmune/collagen disorder; multiple concomitant drug therapy was common, including immunosuppressive therapy in a few cases. Daily doses of captopril in the leukopenic patients were relatively high, particularly in view of their diminished renal function. The neutropenia appeared 3 to 12 weeks after starting captopril; it developed relatively slowly, taking 10 to 30 days to have white blood count fall to its nadir; neutrophils returned to normal in about 2 weeks (other than 2 patients who died of sepsis).

Use captopril with caution in patients with impaired renal function, serious autoimmune disease (particularly SLE), or who are exposed to other drugs known to affect the white cells or immune response. In patients at particular risk (as noted above), perform white blood cell and differential counts prior to therapy, at about 2-week intervals for about the 1st 3 months of therapy, and periodically thereafter.

The risk of neutropenia in patients who are less seriously ill or who receive lower dosages appears to be smaller. In these patients white blood cell counts should be performed every 2 weeks for the 1st 3 months of therapy, and periodically thereafter. Perform differential counts when leukocytes are <4000/mm³ or the pretherapy white count is halved. All patients treated with captopril should be told to report any signs of infection (e.g., sore throat; fever); if infection is suspected, perform counts without delay. Since discontinuation of captopril and other drugs has generally led to prompt return of the white count to normal, upon confirmation of neutropenia (neutrophil count <1000/mm³) withdraw captopril and closely follow the patient's course.

Hypotension—Excessive hypotension was rarely seen in hypertensive patients but is a possibility in severely salt/volume-depleted persons such as those treated vigorously with diuretics (see PRECAUTIONS [Drug Interactions]).

In heart failure, where blood pressure was either normal or low, transient decreases in blood pressure >20% were recorded in about ½ the patients. This transient hypotension may occur after any of the first several doses and is usually well tolerated, although rarely it has been associated with arrhythmia or conduction defects. A starting dose of 6.25 or 12.5 mg tid may minimize the hypotensive effect. Patients should be followed closely for the first 2 weeks of treatment and whenever the dose of captopril and/or diuretic is increased.

BECAUSE OF THE POTENTIAL FALL IN BLOOD PRESSURE IN THESE PATIENTS, THERAPY SHOULD BE STARTED UNDER VERY CLOSE MEDICAL SUPERVISION.

PRECAUTION: General: *Impaired Renal Function,* Hypertension—Some hypertensive patients with renal disease, particularly those with severe renal artery stenosis, have developed increases in BUN and serum creatinine. It may be necessary to reduce captopril dosage and/or discontinue diuretic. For some of these patients, normalization of blood pressure and maintenance of adequate renal perfusion may not be possible. Heart Failure—About 20% of patients develop stable elevations of BUN and serum creatinine >20% above normal or baseline upon long-term treatment. Less than 5% of patients, generally with severe preexisting renal disease, required discontinuation due to progressively increasing creatinine. See DOSAGE AND ADMINISTRATION, ADVERSE REACTIONS [Altered Laboratory Findings]. *Valvular Stenosis*—A theoretical concern, for risk of decreased coronary perfusion, has been noted regarding vasodilator treatment in patients with aortic stenosis, due to decreased afterload reduction.
Surgery/Anesthesia—If hypotension occurs during major surgery or anesthesia, and is considered due to the effects of captopril, it is correctable by volume expansion.

Drug Interactions: *Hypotension. Patients on Diuretic Therapy*—Precipitous reduction of blood pressure may occasionally occur within the 1st 3 hours after administration of the initial captopril dose in patients on diuretics, especially those recently placed on diuretics and those on severe dietary salt restriction or dialysis. This possibility can be minimized by either discontinuing the diuretic or increasing the salt intake about 1 week prior to initiation of captopril therapy. Alternatively, provide medical supervision for at least 3 hours after the initial dose in hypertensive patients.

Agents Having Vasodilator Activity: In heart failure patients vasodilators should be administered with caution.

Agents Causing Renin Release—Captopril's effect will be augmented by antihypertensive agents that cause renin release.

Agents Affecting Sympathetic Activity—The sympathetic nervous system may be especially important in supporting blood pressure in patients receiving captopril alone or with diuretics. Beta-adrenergic blocking drugs add some further antihypertensive effect to captopril, but the overall response is less than additive. Therefore, use agents affecting sympathetic activity (e.g., ganglionic blocking agents or adrenergic neuron blocking agents) with caution.

Agents Increasing Serum Potassium—Give potassium-sparing diuretics or potassium supplements only for documented hypokalemia, and then with caution, since they may lead to a significant increase of serum potassium.

Drug/Laboratory Test Interaction: Captopril may cause a false-positive urine test for acetone.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: Two-year studies with doses of 50 to 1350 mg/kg/day in mice and rats failed to show any evidence of carcinogenic potential. Studies in rats have revealed no impairment of fertility.

Usage in Pregnancy: There are no adequate and well-controlled studies in pregnant women. Embryocidal effects were observed in rabbits. Therefore, captopril should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.

(Continued on adjacent page)

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ACE* INHIBITOR

Capoten®
(captopril tablets)

FOR HYPERTENSION†-PLUS

NEW–BID DOSAGE

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Patients treated for hypertension† may have other disorders that commonly coexist with elevated blood pressure—approximately 14% may have diabetes, 7% asthma, 13% heart failure.[1] Unlike many other antihypertensive agents, CAPOTEN, because of its unique mode of action, is not contraindicated for use in any of these coexisting conditions that frequently complicate hypertension management:

+ DIABETES† (14%)

CAPOTEN does not mask the warning symptoms of hypoglycemia, unlike some beta blockers

+ BRONCHOSPASTIC PULMONARY DISEASE† (7%)

CAPOTEN rarely causes bronchospasm

+ HEART FAILURE† (13%)

CAPOTEN improves cardiac output, unlike beta blockers

MORE PLUSES IN HYPERTENSION-PLUS

*Angiotensin Converting Enzyme

†CAPOTEN is indicated for the treatment of hypertensive patients who on multidrug regimens either have failed to respond satisfactorily or have developed unacceptable side effects.

Please see Precautionary Guidelines for use of CAPOTEN and brief summary of prescribing information accompanying this advertisement.

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"My great, great, great, great grand daddy."

"Slim, trim, wonderful me."

"HOW I LOST MY UGLY FAT."

Years ago, you couldn't find one of my relatives that didn't have a rump that really rolled.

Of course, for years people said they liked us that way.

But then my great, great, great grandmother met an incredibly well-built bull. Just about everything that guy ate turned to good lean muscle. The whole family hasn't been the same since.

Today we're down to a mere nine grams of fat per three-ounce portion. And over half of it's unsaturated. Plus that serving has 192 calories, no more cholesterol than roast chicken without the skin, and all kinds o iron, zinc, B-vitamins and protei

Why, we're even longe and taller than ever before.

In fact, just the other night I met a nutritionist for dinner. And he said that I never looked better.

For a great free recipe booklet featuring lots of lean and low calorie cooking with beef, send your name and address to:

More Light Cooking With Beef, 551 Foster City Boulevard, Suite A, Foster City, California 94404.

*Beef data from 1983 Beef Nutritive Composition Studies conducted by the U.S.D.A. and National Live Stock and Meat Board

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ALLERGY AND IMMUNOLOGY

February 27-March 2—**9th Annual Course: Immunology and the Clinical Practice of Allergy.** UCSD at Vacation Village Resort, San Diego. Wednesday-Sunday. Up to 20 hrs. Contact: UCSD.

March 18-20—**Problem Areas in the Immunization Cycle.** American College of Preventitive Medicine at San Diego. Monday-Wednesday. Contact: National Council for International Health, 2100 Pennsylvania Ave. N.W., Ste. 740, Washington, DC 20073.

April 18-20—**Allergy and Immunology for the Practicing Physician.** UCSF. Thursday-Saturday. 18 hrs. Fee: $200.

ANESTHESIOLOGY

May 5-11—**12th Hawaiian Seminar on Clinical Anesthesia.** California Society of Anesthesiology at Sheraton Kauai Hotel, HA. Sunday-Saturday. 20 hrs. Contact: Education Programs Division, Calif. Society of Anesthesiology, 100 S. Ellsworth Ave., San Mateo, CA. (415) 348-1407.

May 17-22—**Anesthesiology Review Course.** UCSD at Vacation Village, San Diego. Friday-Wednesday. 38 hrs.

CANCER

March 1-2—**Cancer and the Elderly.** West Coast Cancer Foundation at Sheraton Palace Hotel, San Francisco. Friday-Saturday. 12 hrs. Fee: $150. Contact: West Coast Cancer Foundation, 50 Francisco, San Francisco 94133.

March 22—**One Day Cancer Screening and Flexible Sigmoidoscopy Workshop.** Continuing Medical Education Associates at Holiday Inn Union Square, San Francisco. Friday. 7 hrs. Fee: $135. Contact: J. Shiller. CMEA, PO Box 84296, San Diego 92138.

March 24—**One Day Colon Cancer Screening and Flexible Sigmoidoscopy.** Continuing Medical Education Associates at Kona Kai Club, San Diego, Sunday. 7 hrs. Fee: $135. Contact: J. Shiller, CMEA, PO Box 84296, San Diego 92138.

April 6-8—**Diagnosis and Management of the Malignant Melanoma.** UCSF. Thursday-Saturday. 11 hrs. Fee: $250.

CARDIOLOGY

February 18-22—**Non-Invasive Diagnostic Techniques in Vascular Disease.** Scripps Clinic and Research Foundation at Sheraton Harbor Island Hotel, San Diego. Monday-Friday. 35 hrs. Contact: Nomi Feldman, Conference Coord., 3770 Tansy, San Diego, 92121. (619) 453-6222.

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 44 Gough Street, San Francisco 94103. (415) 863-5522.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Flora Harlee-Cordett, MS, MPH, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr., MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, ext. 2400.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 563-4321, ext. 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 497-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0328.

UCI: University of California, Irvine
Contact: E. R. Jennings, MD, Assistant Dean, University of California, Irvine, California College of Medicine, c/o UCI/CME Program, Memorial Hospital Medical Center, 2801 Atlantic Avenue, Long Beach 90801. (213) 595-3837, or (714) 856-5414, UCI Extension.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 452-3940.

UCSF: University of California, San Francisco
Contact: David S. Gullion, MD, Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 224-7051.

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There are doctors who say that generic drugs have a place in their practice—but not necessarily in the treatment of serious or potentially life-threatening disease. And when they consider that the average patient pays only about 45¢ a day for INDERAL (propranolol HCl) Tablets, there's not much left to discuss.

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Please see next page for brief summary of prescribing information.

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Small price to pay.

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10 mg 20 mg 40 mg 60 mg 80 mg 90 mg*

BRIEF SUMMARY (FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE CIRCULAR.)

INDERAL® (propranolol hydrochloride) Tablets

CONTRAINDICATIONS

INDERAL is contraindicated in 1) cardiogenic shock, 2) sinus bradycardia and greater than first degree block, 3) bronchial asthma 4) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL.

WARNINGS

CARDIAC FAILURE Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta blockade may precipitate more severe failure. Although beta blockers should be avoided in overt congestive heart failure, if necessary they can be used with close follow-up in patients with a history of failure who are well compensated and are receiving digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle.

IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta blockers can, in some cases, lead to cardiac failure. Therefore, at the first sign or symptom of heart failure, the patient should be digitalized and/or treated with diuretics, and the response observed closely; or INDERAL should be discontinued (gradually, if possible).

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following abrupt discontinuance of INDERAL therapy. Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced over at least a few weeks and the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)—PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

MAJOR SURGERY The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

INDERAL, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in starting and maintaining the heartbeat has also been reported with beta blockers.

DIABETES AND HYPOGLYCEMIA Beta-adrenergic blockade may prevent the appearance of certain premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia in labile insulin-dependent diabetes. In these patients, it may be more difficult to adjust the dosage of insulin.

THYROTOXICOSIS Beta blockade may mask certain clinical signs of hyperthyroidism. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

PRECAUTIONS

General: Propranolol should be used with caution in patients with impaired hepatic or renal function. INDERAL is not indicated for the treatment of hypertensive emergencies.

Beta-adrenoreceptor blockade can cause reduction of intraocular pressure. Patients should be told that INDERAL (propranolol hydrochloride) may interfere with the glaucoma screening test. Withdrawal may lead to a return of increased intraocular pressure.

Clinical Laboratory Tests. Elevated blood urea levels in patients with severe heart disease; elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

DRUG INTERACTIONS Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if INDERAL is administered. The added catecholamine-blocking action may produce an excessive reduction of resting sympathetic nervous activity which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In 18-month studies in both rats and mice, employing doses up to 150 mg/kg/day, there was no evidence of significant drug-induced toxicity. There were no drug-related tumorigenic effects at any of the dosage levels. Reproductive studies in animals did not show any impairment of fertility that was attributable to the drug.

Pregnancy Pregnancy Category C. INDERAL has been shown to be embryotoxic in animal studies at doses about 10 times greater than the maximum recommended human dose.

There are no adequate and well-controlled studies in pregnant women. INDERAL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: INDERAL is excreted in human milk. Caution should be exercised when INDERAL is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Most adverse effects have been mild and transient and have rarely required the withdrawal of therapy.

Cardiovascular bradycardia, congestive heart failure; intensification of AV block, hypotension; paresthesia of hands, thrombocytopenic purpura; arterial insufficiency, usually of the Raynaud type.

Central Nervous System Lightheadedness; mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia, visual disturbances, hallucinations, an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Gastrointestinal nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis.

Allergic pharyngitis and agranulocytosis, erythematous rash, fever combined with chills and sore throat, laryngospasm and respiratory distress.

Respiratory bronchospasm.

Hematologic agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Auto-Immune In extremely rare instances, systemic lupus erythematosus has been reported.

Miscellaneous alopecia, LE-like reactions, psoriasiform rashes, dry eyes, male impotence, and Peyronie's disease have been reported rarely. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been associated with propranolol.

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(Continued from Page 161)

February 22-24—**Coronary Artery Disease and Sudden Death: Primary and Secondary Prevention.** International Medical Education Corp. at Americana Canyon, Palm Springs. Friday-Sunday. 13 hrs. Fee: $295. Contact: IMEC, 64 Inverness Dr. E, Englewood, CO 80112.

March 1-3—**ECG Interpretation and Arrhythmia Management.** International Medical Corp. at Desert Inn, Las Vegas. Friday-Sunday. 13 hrs. Fee: $295. Contact: IMEC, 64 Inverness Dr. E, Englewood, CO 80112.

March 6-8—**2nd Annual Professional Symposium on Acute Cardiopulmonary Disease.** Mercy Hospital of Sacramento at Ahwahnee Hotel, Yosemite. Wednesday-Friday. 13 hrs. Contact Joan Willis, Mercy Hospital, (916) 456-3365.

March 10-14—**34th Annual Scientific Session of the American College of Cardiology** at Anaheim. Sunday-Thursday. Contact: ACC, 9111 Old Georgetown Rd., Bethesda, MD 20814, (301) 897-5400.

March 13—**Cardiology: Arrhythmias—Recognition and Treatment.** LLU. Wednesday. 4 hrs.

March 15—**Reider Laser Symposium in Cardiology.** UCI. Friday. 3 hrs.

March 16—**Cardiac Lecture Series: "Cardiovascular Trauma Texas Style."** Heart Institute of the Desert at Annenberg Center, Rancho Mirage. Saturday. 2 hrs. Contact: Eisenhower Medical Center, 39000 Bob Hope Dr., Rancho Mirage, CA 92270.

March 18—**The Richard J. Bing Symposium IV—Cardiology 1985.** Huntington Memorial Hospital. Monday. 5.5 hrs. Fee: $35. Contact: Huntington Memorial Hospital, 100 Congress St., PO Box 7013, Pasadena 91109-7013.

March 22-24—**Cardiology for the Primary Care Physician.** UCSD at Palm Springs Spa Hotel. Friday-Sunday. 18 hrs.

March 23—**Reider Laser Symposium in Pulmonary Medicine.** UCI. Saturday. 7 hrs.

March 25-29—**Vascular and Pulmonary Diseases: Diagnosis & Management.** Medical Education Resources at Sheraton Maui, HI. 13 hrs. Fee: $275. Contact: Leslie Shaffer, Medical Education Resources, 5808 S. Rapp St., Ste 202, Littleton, CO 80120. (303) 798-9682.

March 29-31—**Vascular and Pulmonary Disease: Diagnosis and Management.** University of Colorado at Desert Inn, Las Vegas. Friday-Sunday. 13 hrs. Contact: Medical Education Resources, 5808 S. Rapp St., Ste. 202, Littleton, CO 80120. (800) 421-3756.

April 6—**Cardiac Lecture Series: The Ideal Conduit.** Heart Institute of the Desert at Annenberg Center, Rancho Mirage. Saturday. 2 hrs. Contact: Eisenhower Medical Center, 39000 Bob Hope Dr., Rancho Mirage 92270.

April 10-13—**1st Annual Program—Two Dimensional Echocardiography: Core Curriculum and Self-Assessment.** American College of Cardiology at Sheraton Harbor Island East, San Diego. Wednesday-Saturday. Contact: ACC, 9111 Old Georgetown Rd., Bethesda, MD 20814.

April 15-19—**ECG Interpretation and Arrhythmia Management.** International Medical Education Corp. at Marriott Hotel, Maui. Monday-Friday. 13 hrs. Fee: $295. Contact: IMEC, 64 Inverness Dr. East, Englewood, CO 80112.

April 20—**Cardiac Lecture Series: Advances in Research.** Heart Institute of the Desert at Annenberg Center, Rancho Mirage. Saturday. 2 hrs. Contact: Eisenhower Medical Center, 39000 Bob Hope Dr., Rancho Mirage 92270. (619) 568-2900.

April 26-28—**Coronary Artery Disease and Sudden Death: Primary and Secondary Prevention.** International Medical Education Corp. at Hyatt Union Square, San Francisco. Friday-Sunday. 13 hrs. Fee: $295. Contact: IMEC, 64 Inverness Dr. East, Englewood, CO 80112

April 26-28—**Vascular and Pulmonary Disease: Diagnosis and Management.** Medical Education Resources at Renaissance Hotel, San Francisco. Friday-Sunday. 13 hrs. Fee: $275. Contact: Leslie Shaffer, Medical Education Res., 5808 S. Rapp St., Ste 202, Littleton, CO 80120. (303) 798-9862.

May 10-12—**Coronary Artery Disease and Sudden Death: Primary and Secondary Prevention.** International Medical Education Corp. at Hyatt Islandia, San Diego. Friday-Sunday. Contact: IMEC, Div. of Postgraduate & Continuing Medical Education, 64 Inverness Dr. E., Englewood, CO 80112.

EMERGENCY MEDICINE

February 25-28—**Critical Care Medicine.** USC at MGM Grand Hotel, Las Vegas. Monday-Thursday. Contact: USC.

March 10-15—**6th Annual Mammoth Mountain Emergency Medicine Ski Conference.** UCI and Medical Conferences at Mammoth Lakes. Sunday-Friday. 20 hrs. Fee: $325. Contact: Med. Conf. Inc., PO Box 52-B, Newport Beach 92662. (714) 650-4156.

March 11-15—**Postgraduate Institute for Emergency Physicians, Symposium II.** UCSD at La Jolla Village Inn, La Jolla. Monday-Friday. 13-36 hrs. Fee: $200-675.

April 6-13—**Emergency Medicine—1985.** USC at Royal Lahaina Hotel, Maui. One week. 26.5 hrs. Fee: $495.

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References:
1. Strauss WE, McIntyre KM, Parisi AF, et al: Safety and efficacy of diltiazem hydrochloride for the treatment of stable angina pectoris: Report of a cooperative clinical trial. Am J Cardiol 49:560-566, 1982.
2. Pool PE, Seagren SC, Bonanno JA, et al: The treatment of exercise-inducible chronic stable angina with diltiazem: Effect on treadmill exercise. Chest 78 (July suppl):234-238, 1980.

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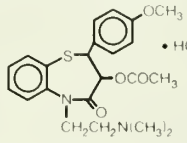
DESCRIPTION

CARDIZEM® (diltiazem hydrochloride) is a calcium ion influx inhibitor (slow channel blocker or calcium antagonist). Chemically, diltiazem hydrochloride is 1,5-Benzothiazepin-4(5H)one,3-(acetyloxy) -5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-, monohydrochloride,(+) -cis- The chemical structure is:



Diltiazem hydrochloride is a white to off-white crystalline powder with a bitter taste. It is soluble in water, methanol, and chloroform. It has a molecular weight of 450.98. Each tablet of CARDIZEM contains either 30 mg or 60 mg diltiazem hydrochloride for oral administration.

CLINICAL PHARMACOLOGY

The therapeutic benefits achieved with CARDIZEM are believed to be related to its ability to inhibit the influx of calcium ions during membrane depolarization of cardiac and vascular smooth muscle.

Mechanisms of Action. Although precise mechanisms of its antianginal actions are still being delineated, CARDIZEM is believed to act in the following ways:

1. Angina Due to Coronary Artery Spasm: CARDIZEM has been shown to be a potent dilator of coronary arteries both epicardial and subendocardial. Spontaneous and ergonovine-induced coronary artery spasm are inhibited by CARDIZEM.
2. Exertional Angina: CARDIZEM has been shown to produce increases in exercise tolerance, probably due to its ability to reduce myocardial oxygen demand. This is accomplished via reductions in heart rate and systemic blood pressure at submaximal and maximal exercise work loads.

In animal models, diltiazem interferes with the slow inward (depolarizing) current in excitable tissue. It causes excitation-contraction uncoupling in various myocardial tissues without changes in the configuration of the action potential. Diltiazem produces relaxation of coronary vascular smooth muscle and dilation of both large and small coronary arteries at drug levels which cause little or no negative inotropic effect. The resultant increases in coronary blood flow (epicardial and subendocardial) occur in ischemic and nonischemic models and are accompanied by dose-dependent decreases in systemic blood pressure and decreases in peripheral resistance.

Hemodynamic and Electrophysiologic Effects. Like other calcium antagonists, diltiazem decreases sinoatrial and atrioventricular conduction in isolated tissues and has a negative inotropic effect in isolated preparations. In the intact animal, prolongation of the AH interval can be seen at higher doses.

In man, diltiazem prevents spontaneous and ergonovine-provoked coronary artery spasm. It causes a decrease in peripheral vascular resistance and a modest fall in blood pressure and, in exercise tolerance studies in patients with ischemic heart disease, reduces the heart rate-blood pressure product for any given work load. Studies to date, primarily in patients with good ventricular function, have not revealed evidence of a negative inotropic effect, cardiac output, ejection fraction, and left ventricular end diastolic pressure have not been affected. There are as yet few data on the interaction of diltiazem and beta-blockers. Resting heart rate is usually unchanged or slightly reduced by diltiazem.

Intravenous diltiazem in doses of 20 mg prolongs AH conduction time and AV node functional and effective refractory periods approximately 20%. In a study involving single oral doses of 300 mg of CARDIZEM in six normal volunteers, the average maximum PR prolongation was 14% with no instances of greater than first-degree AV block. Diltiazem-associated prolongation of the AH interval is not more pronounced in patients with first-degree heart block. In patients with sick sinus syndrome, diltiazem significantly prolongs sinus cycle length (up to 50% in some cases).

Chronic oral administration of CARDIZEM in doses of up to 240 mg/day has resulted in small increases in PR interval, but has not usually produced abnormal prolongation. There were, however, three instances of second-degree AV block and one instance of third-degree AV block in a group of 959 chronically treated patients.

Pharmacokinetics and Metabolism. Diltiazem is absorbed from the tablet formulation to about 80% of a reference capsule and is subject to an extensive first-pass effect, giving an absolute bioavailability (compared to intravenous dosing) of about 40%. CARDIZEM undergoes extensive hepatic metabolism in which 2% to 4% of the unchanged drug appears in the urine. In vitro binding studies show CARDIZEM is 70% to 80% bound to plasma proteins. Competitive ligand binding studies have also shown CARDIZEM binding is not altered by therapeutic concentrations of digoxin, hydrochlorothiazide, phenylbutazone, propranolol, salicylic acid, or warfarin. Single oral doses of 30 to 120 mg of CARDIZEM result in detectable plasma levels within 30 to 60 minutes and peak plasma levels two to three hours after drug administration. The plasma elimination half-life following single or multiple drug administration is approximately 3.5 hours. Desacetyl diltiazem is also present in the plasma at levels of 10% to 20% of the parent drug and is 25% to 50% as potent a coronary vasodilator as diltiazem. Therapeutic blood levels of CARDIZEM appear to be in the range of 50 to 200 ng/ml. There is a departure from dose-linearity when single doses above 60 mg are given; a 120-mg dose gave blood levels three times that of the 60-mg dose. There is no information about the effect of renal or hepatic impairment on excretion or metabolism of diltiazem.

INDICATIONS AND USAGE

1. **Angina Pectoris Due to Coronary Artery Spasm.** CARDIZEM is indicated in the treatment of angina pectoris due to coronary artery spasm. CARDIZEM has been shown effective in the treatment of spontaneous coronary artery spasm presenting as Prinzmetal's variant angina (resting angina with ST-segment elevation occurring during attacks).
2. **Chronic Stable Angina (Classic Effort-Associated Angina).** CARDIZEM is indicated in the management of chronic stable angina. CARDIZEM has been effective in controlled trials in reducing angina frequency and increasing exercise tolerance.

There are no controlled studies of the effectiveness of the concomitant use of diltiazem and beta-blockers or of the safety of this combination in patients with impaired ventricular function or conduction abnormalities.

CONTRAINDICATIONS

CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker, and (3) patients with hypotension (less than 90 mm Hg systolic).

WARNINGS

1. **Cardiac Conduction.** CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (six of 1243 patients for 0.48%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.
2. **Congestive Heart Failure.** Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). Experience with the use of CARDIZEM alone or in combination with beta-blockers in patients with impaired ventricular function is very limited. Caution should be exercised when using the drug in such patients.
3. **Hypotension.** Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.
4. **Acute Hepatic Injury.** In rare instances, patients receiving CARDIZEM have exhibited reversible acute hepatic injury as evidenced by moderate to extreme elevations of liver enzymes. (See PRECAUTIONS and ADVERSE REACTIONS.)

PRECAUTIONS

General. CARDIZEM (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any new drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Drug Interaction. Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS).

Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers or digitalis is usually well tolerated. Available data are not sufficient, however, to predict the effects of concomitant treatment, particularly in patients with left ventricular dysfunction or cardiac conduction abnormalities. In healthy volunteers, diltiazem has been shown to increase serum digoxin levels up to 20%.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response in in vitro bacterial tests. No intrinsic effect on fertility was observed in rats.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

There are no well-controlled studies in pregnant women; therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when CARDIZEM is administered to a nursing woman if the drug's benefits are thought to outweigh its potential risks in this situation.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded.

In domestic placebo-controlled trials, the incidence of adverse reactions reported during CARDIZEM therapy was not greater than that reported during placebo therapy.

The following represent occurrences observed in clinical studies which can be at least reasonably associated with the pharmacology of calcium influx inhibition. In many cases, the relationship to CARDIZEM has not been established. The most common occurrences, as well as their frequency of presentation, are: edema (2.4%), headache (2.1%), nausea (1.9%), dizziness (1.5%), rash (1. asthenia (1.2%), AV block (1.1%). In addition, the following ev were reported infrequently (less than 1%) with the order of pres tion corresponding to the relative frequency of occurrence.

Cardiovascular:	Flushing, arrhythmia, hypotension, brad dia, palpitations, congestive heart fa syncope.
Nervous System:	Paresthesia, nervousness, somnole tremor, insomnia, hallucinations, and amn
Gastrointestinal	Constipation, dyspepsia, diarrhea, vom mild elevations of alkaline phosphatase, S SGPT, and LDH.
Dermatologic:	Pruritus, petechiae, urticaria, photosensi
Other:	Polyuria, nocturia.

The following additional experiences have been noted:

A patient with Prinzmetal's angina experiencing episod vasospastic angina developed periods of transient asympto asystole approximately five hours after receiving a single 6 dose of CARDIZEM.

The following postmarketing events have been reported quently in patients receiving CARDIZEM: erythema multiforme kopenia; and extreme elevations of alkaline phosphatase, S SGPT, LDH, and CPK. However, a definitive cause and effect bet these events and CARDIZEM therapy is yet to be established.

OVERDOSAGE OR EXAGGERATED RESPONSE

Overdosage experience with oral diltiazem has been lin Single oral doses of 300 mg of CARDIZEM have been well tole by healthy volunteers. In the event of overdosage or exagge response, appropriate supportive measures should be employ addition to gastric lavage. The following measures may be consic

Bradycardia	Administer atropine (0.60 to 1.0 mg). If is no response to vagal blockade, admi isoproterenol cautiously.
High-Degree AV Block	Treat as for bradycardia above. Fixed degree AV block should be treated with diac pacing.
Cardiac Failure	Administer inotropic agents (isoprote dopamine, or dobutamine) and diuretics.
Hypotension	Vasopressors (eg, dopamine or levarte bitartrate).

Actual treatment and dosage should depend on the severity clinical situation and the judgment and experience of the tre physician.

The oral/LD_{50}'s in mice and rats range from 415 to 740 m and from 560 to 810 mg/kg, respectively. The intravenous LD these species were 60 and 38 mg/kg, respectively. The oral L dogs is considered to be in excess of 50 mg/kg, while lethalit seen in monkeys at 360 mg/kg. The toxic dose in man is not k but blood levels in excess of 800 ng/ml have not been assoc with toxicity.

DOSAGE AND ADMINISTRATION

Exertional Angina Pectoris Due to Atherosclerotic I nary Artery Disease or Angina Pectoris at Rest Due to I nary Artery Spasm. Dosage must be adjusted to each pa needs. Starting with 30 mg four times daily, before meals a bedtime, dosage should be increased gradually (given in di doses three or four times daily) at one- to two-day intervals optimum response is obtained. Although individual patients respond to any dosage level, the average optimum dosage appears to be 180 to 240 mg/day. There are no available data co ing dosage requirements in patients with impaired renal or h function. If the drug must be used in such patients, titration sho carried out with particular caution.

Concomitant Use With Other Antianginal Agents:

1. **Sublingual NTG** may be taken as required to abort anginal attacks during CARDIZEM therapy.
2. **Prophylactic Nitrate Therapy**—CARDIZEM may be coadministered with short- and long-acting nitrates, but have been no controlled studies to evaluate the antia effectiveness of this combination.
3. **Beta-blockers.** (See WARNINGS and PRECAUTIONS.)

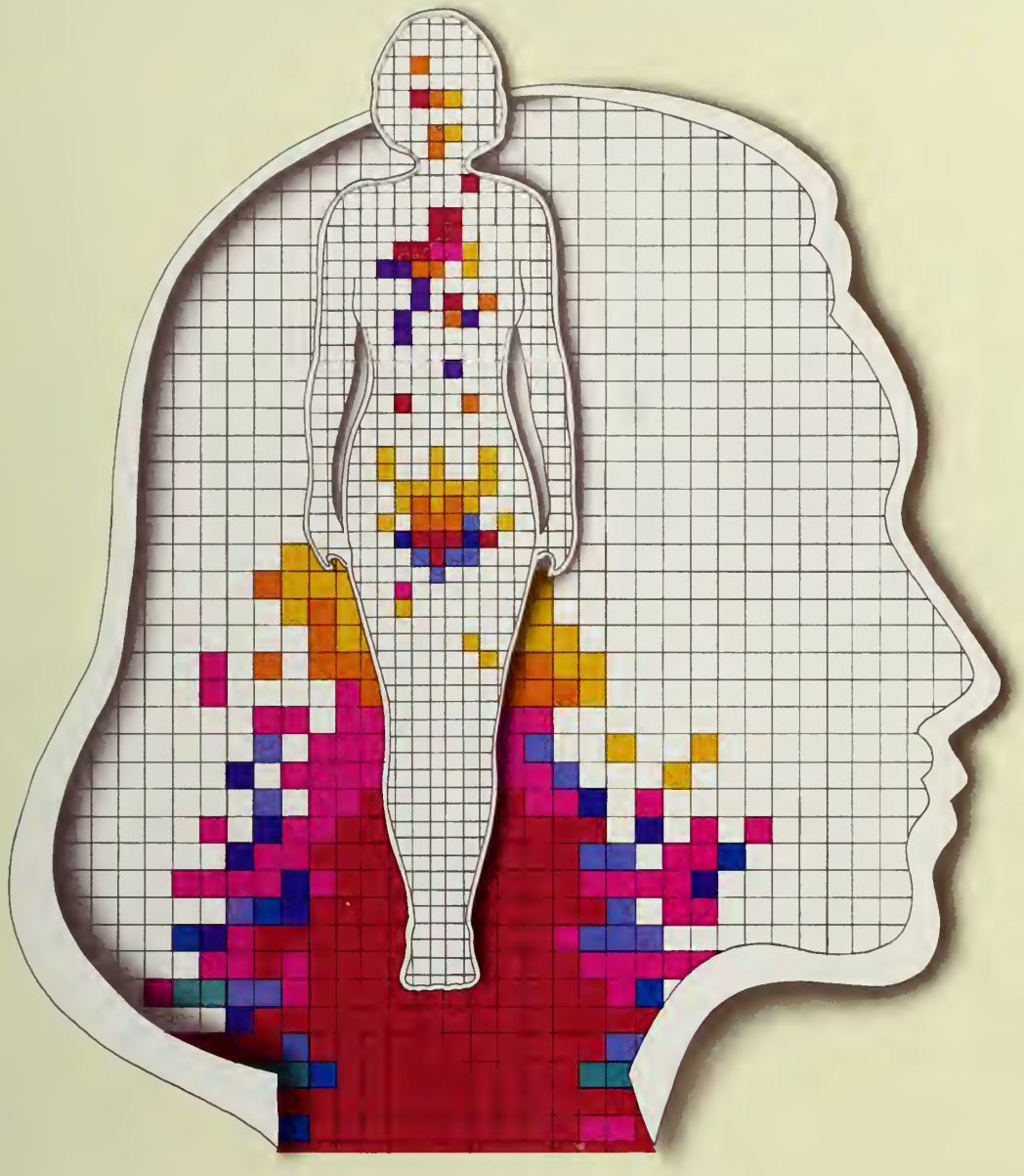
HOW SUPPLIED

Cardizem 30-mg tablets are supplied in bottles of 100 0088-1771-47) and in Unit Dose Identification Paks of 100 0088-1771-49). Each green tablet is engraved with MARION o side and 1771 engraved on the other. CARDIZEM 60-mg s tablets are supplied in bottles of 100 (NDC 0088-1772-47) and Dose Identification Paks of 100 (NDC 0088-1772-49). Each tablet is engraved with MARION on one side and 1772 on the

Issued 4.

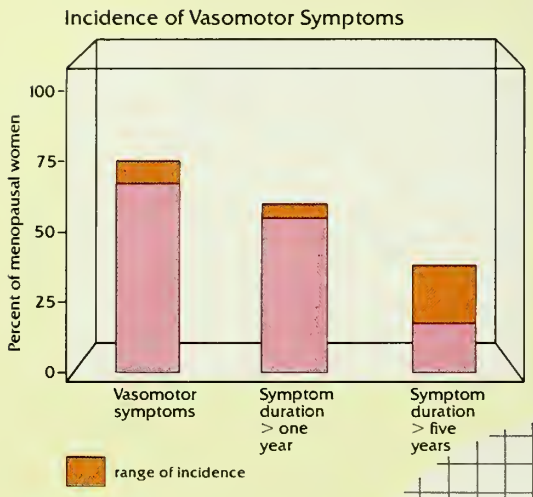
Another patient benefit product from

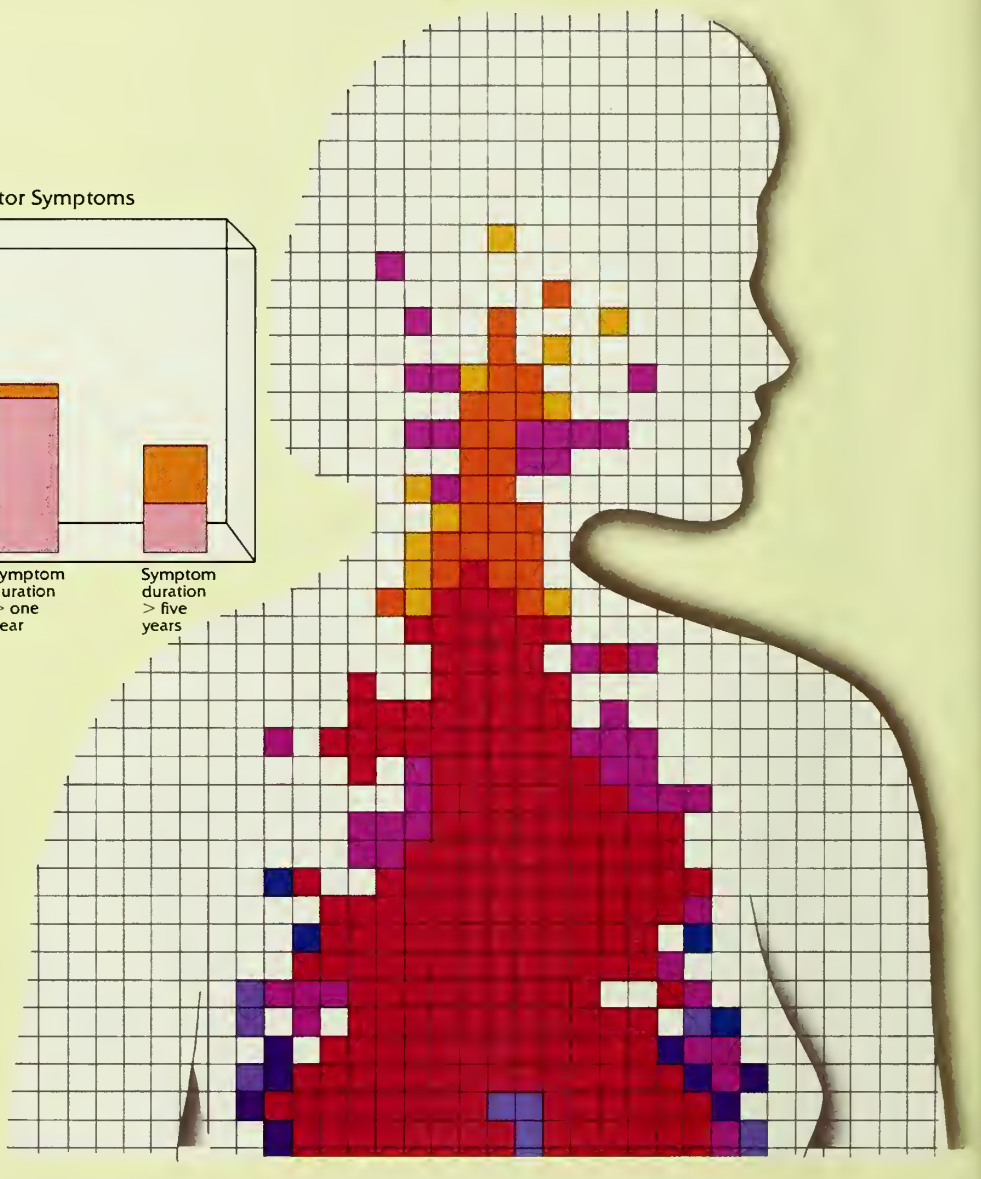
PHARMACEUTICAL DIVISION
MARION LABORATORIES, INC.
KANSAS CITY, MISSOURI 64137



THE ENDOCRINOLOGY OF AGING
Three profiles

VASOMOTOR SYMPTOMS THAT DEMAND INTERVENTION





PREMARIN RELIEVES MODERATE TO SEVERE VASOMOTOR SYMPTOMS

Vasomotor symptoms are the most common manifestation of the menopause, affecting up to 75% of menopausal women. Of these, 80% may suffer for more than a year and up to 50% for more than five years.[1] These symptoms can disrupt a woman's life by chronically interrupting sleep, resulting in anxiety and irritability.

In a study of postmenopausal women suffering severe episodes of cutaneous flushing, symptoms improved markedly after administration of estrogen[2]—the treatment of choice for moderate to severe vasomotor symptoms.[3] The estrogen of choice is PREMARIN, the most widely prescribed estrogen for over 40 years. PREMARIN (Conjugated Estrogens Tablets, U.S.P.) relieves moderate to severe vasomotor symptoms of the natural menopause, as well as the acute and often severe symptoms of surgical menopause.

PREMARIN®

(CONJUGATED ESTROGENS TABLETS, U.S.P.)

0.3 mg 0.625 mg 0.9 mg 1.25 mg 2.5 mg

Please see last page for brief summary of full prescribing information.

VAGINAL ATROPHY THAT INTERFERES WITH SEXUALITY

PREMARIN RESTORES THE VAGINAL ENVIRONMENT

In the postmenopausal woman, decreasing levels of estrogen can have devastating effects on a woman's sexual functioning. The pH of vaginal secretions rises, promoting the growth of contaminating organisms. The vaginal epithelium dries and thins, becoming susceptible to irritation, injury, and infection. Sexual relations may be difficult or impossible.

PREMARIN (Conjugated Estrogens, U.S.P.) Vaginal Cream focuses therapy at the site of the problem. Vaginal dryness is relieved, pH reverts to its normal acidity, and the epithelium thickens and becomes more resistant to injury and infection. With the vaginal environment returned to its premenopausal state, sexual function may improve.

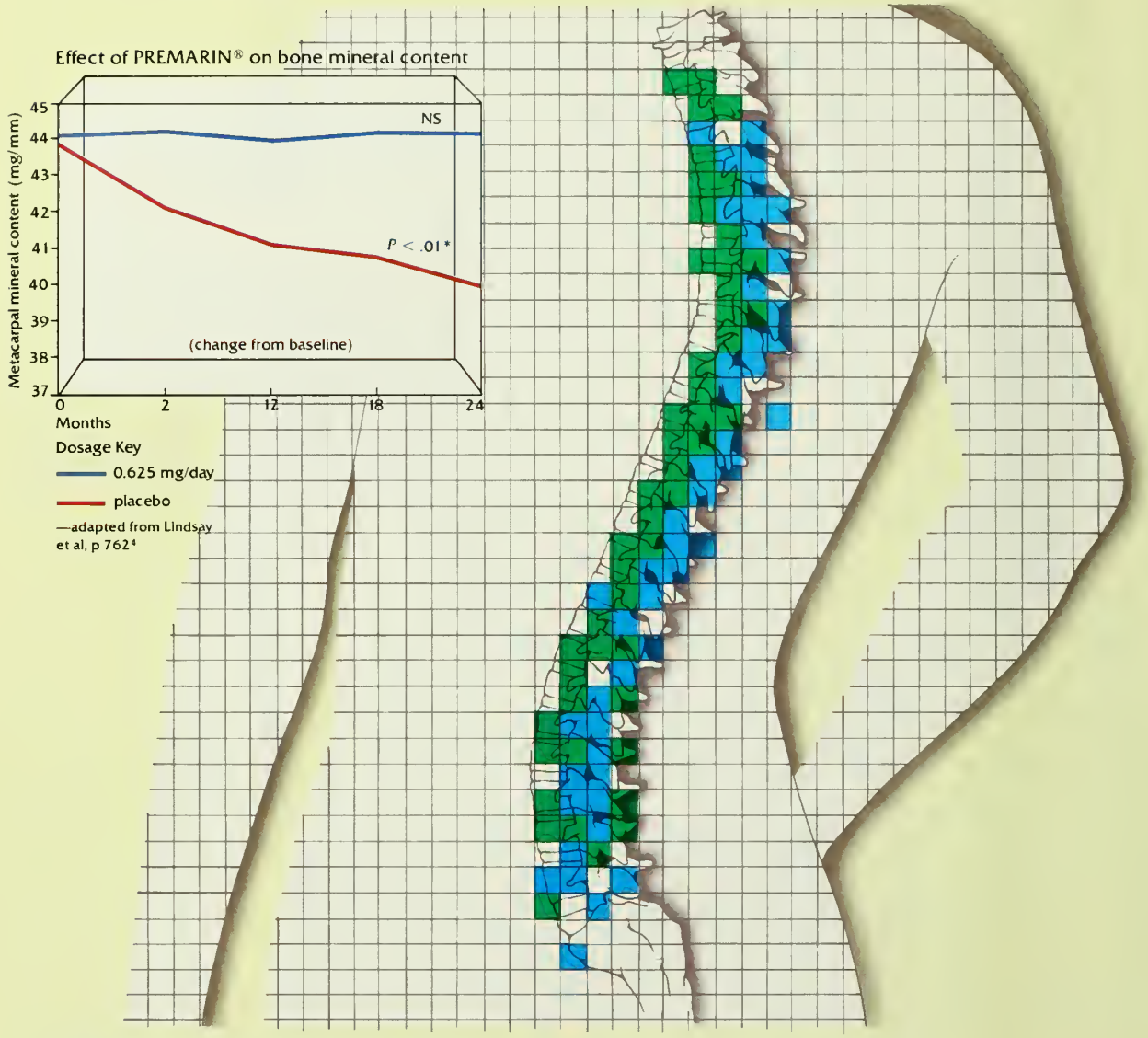
PREMARIN®

(CONJUGATED ESTROGENS, U.S.P.) Vaginal Cream

0.625 mg/g

Please see last page for brief summary of full prescribing information.

POSTMENOPAUSAL BONE LOSS THAT INCAPACITATES

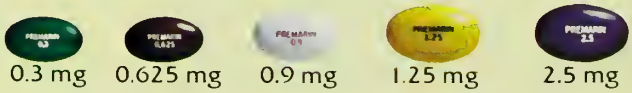


PREMARIN MAY HALT THE DISABLING COURSE OF OSTEOPOROSIS*

Osteoporosis has an enormous epidemiological impact: it affects 10 million American women, and 26% of all women over age 60.[5] The disease begins silently and progresses inexorably for 15 to 20 years, until disabling complications occur.[6]

To minimize osteoporotic damage, the condition must be detected early and treated promptly. For many patients, PREMARIN is optimal therapy for osteoporosis, as part of a comprehensive program that includes exercise, good nutrition, and calcium supplements. In a controlled study of postmenopausal and oophorectomized women, PREMARIN (Conjugated Estrogens Tablets, U.S.P.) doses of 0.625 mg/day prevented loss of metacarpal mineral content (see graph above).

PREMARIN®
(CONJUGATED ESTROGENS TABLETS, U.S.P.)



0.3 mg 0.625 mg 0.9 mg 1.25 mg 2.5 mg

*Conjugated Estrogens Tablets have been evaluated as probably effective for treating estrogen-deficiency-induced osteoporosis.

Please see last page for brief summary of full prescribing information.

EF SUMMARY *(FOR FULL PRESCRIBING INFORMATION AND PATIENT INFORMATION, SEE KAGE CIRCULAR)*

EMARIN® Brand of Conjugated Estrogens Tablets, U.S.P.
EMARIN® Brand of Conjugated Estrogens, U.S.P. Vaginal Cream in a nonliquefying base

ESTROGENS HAVE BEEN REPORTED TO INCREASE THE RISK OF ENDOMETRIAL CARCINOMA.

Three independent case control studies have reported an increased risk of endometrial cancer n postmenopausal women exposed to exogenous estrogens for more than one year This risk vas independent of the other known risk factors for endometrial cancer. These studies are urther supported by the finding that incidence rates of endometrial cancer have increased harply since 1969 in eight different areas of the United States with population-based cancer eporting systems, an increase which may be related to the rapidly expanding use of estrogens during the last decade. The three case control studies reported that the risk of endometrial cancer in estrogen users was about 4 5 to 13 9 times greater than in nonusers. The risk appears o depend on both duration of treatment and on estrogen dose. In view of these findings, when estrogens are used for the treatment of menopausal symptoms, the lowest dose that will control symptoms should be utilized and medication should be discontinued as soon as possible When prolonged treatment is medically indicated, the patient should be reassessed on at least a semiannual basis to determine the need for continued therapy. Although the evidence must be considered preliminary, one study suggests that cyclic administration of low doses of estrogen may carry less risk than continuous administration; it therefore appears prudent to utilize such a regimen. Close clinical surveillance of all women taking estrogens is important. In all cases of undiagnosed persistent or recurring abnormal vaginal bleeding, adequate diagnostic measures should be undertaken to rule out malignancy. There is no evidence at present that "natural" estrogens are more or less hazardous than "synthetic" estrogens at equiestrogenic doses.

2. ESTROGENS SHOULD NOT BE USED DURING PREGNANCY.

The use of female sex hormones, both estrogens and progestogens, during early pregnancy may seriously damage the offspring It has been shown that females exposed in utero to diethylstilbestrol, a non-steroidal estrogen, have an increased risk of developing in later life a form of vaginal or cervical cancer that is ordinarily extremely rare. This risk has been estimated as not greater than 4 per 1000 exposures. Furthermore, a high percentage of such exposed women (from 30 to 90 percent) have been found to have vaginal adenosis, epithelial changes of the vagina and cervix Although these changes are histologically benign, it is not known whether they are precursors of malignancy Although similar data are not available with the use of other estrogens, it cannot be presumed they would not induce similar changes. Several reports suggest an association between intrauterine exposure to female sex hormones and congenital anomalies, including congenital heart defects and limb reduction defects. One case control study estimated a 4 7-fold increased risk of limb reduction defects in infants exposed in utero to sex hormones (oral contraceptives, hormone withdrawal tests for pregnancy, or attempted treatment for threatened abortion). Some of these exposures were very short and involved only a few days of treatment. The data suggest that the risk of limb reduction defects in exposed fetuses is somewhat less than 1 per 1000. In the past, female sex hormones have been used during pregnancy in an attempt to treat threatened or habitual abortion. There is considerable evidence that estrogens are ineffective for these indications, and there is no evidence from well controlled studies that progestogens are effective for these uses. If PREMARIN is used during pregnancy, or if the patient becomes pregnant while taking this drug, she should be apprised of the potential risks to the fetus, and the advisability of pregnancy continuation

SCRIPTION: PREMARIN (Conjugated Estrogens, U.S.P.) contains a mixture of estrogens, tained exclusively from natural sources, blended to represent the average composition of material rived from pregnant mares' urine. It contains estrone, equilin, and 17α-dihydroequilin, together h smaller amounts of 17α-estradiol, equilenin, and 17α-dihydroequilenin as salts of their sulfate ers.

INDICATIONS: Based on a review of PREMARIN Tablets by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications for use as follows:

Effective: 1. Moderate to severe vasomotor symptoms associated with the menopause (There is no evidence that estrogens are effective for nervous symptoms or depression without associated vasomotor symptoms, and they should not be used to treat such conditions.)

2. Atrophic vaginitis
3. Kraurosis vulvae
4. Female hypogonadism
5. Female castration
6. Primary ovarian failure
7. Breast cancer (for palliation only) in appropriately selected women and men with metastatic disease.
8. Prostatic carcinoma—palliative therapy of advanced disease.
9. Postpartum breast engorgement—Although estrogens have been widely used for the prevention of postpartum breast engorgement, controlled studies have demonstrated that the incidence of significant painful engorgement in patients not receiving such hormonal therapy is low and usually responsive to appropriate analgesic or other supportive therapy. Consequently, the benefit to be derived from estrogen therapy for this indication must be carefully weighed against the potential increased risk of puerperal thromboembolism associated with the use of large doses of estrogens.

PREMARIN HAS NOT BEEN SHOWN TO BE EFFECTIVE FOR ANY PURPOSE DURING PREGNANCY AND ITS USE MAY CAUSE SEVERE HARM TO THE FETUS (SEE BOXED WARNING).

"Probably" effective: For estrogen deficiency-induced osteoporosis, and only when used in conjunction with other important therapeutic measures such as diet, calcium, physiotherapy, and good general health-promoting measures. Final classification of this indication requires further investigation.

DICATIONS: PREMARIN (Conjugated Estrogens, U.S.P.) Vaginal Cream is indicated in the eatment of atrophic vaginitis and kraurosis vulvae. PREMARIN Vaginal Cream HAS NOT BEEN OWN TO BE EFFECTIVE FOR ANY PURPOSE DURING PREGNANCY AND ITS USE MAY CAUSE VERE HARM TO THE FETUS (SEE BOXED WARNING).

ONTRAINDICATIONS: Estrogens should not be used in women (or men) with any of the following nditions: 1. Known or suspected cancer of the breast except in appropriately selected patients ing treated for metastatic disease. 2. Known or suspected estrogen-dependent neoplasia Known or suspected pregnancy (See Boxed Warning). 4. Undiagnosed abnormal genital bleeding Active thrombophlebitis or thromboembolic disorders. 6. A past history of thrombophlebitis, rombosis, or thromboembolic disorders associated with previous estrogen use (except when used treatment of breast or prostatic malignancy).

ARNINGS: Long term continuous administration of natural and synthetic estrogens in certain imal species increases the frequency of carcinomas of the breast, cervix, vagina, and liver There e now reports that estrogens increase the risk of carcinoma of the endometrium in humans. (See oxed Warning.) At the present time there is no satisfactory evidence that estrogens given to ostmenopausal women increase the risk of cancer of the breast, although a recent study has raised is possibility There is a need for caution in prescribing estrogens for women with a strong family story of breast cancer or who have breast nodules, fibrocystic disease, or abnormal mammograms recent study has reported a 2- to 3-fold increase in the risk of surgically confirmed gallbladder sease in women receiving postmenopausal estrogens.

Adverse effects of oral contraceptives may be expected at the larger doses of estrogen used to treat ostatic or breast cancer or postpartum breast engorgement; it has been shown that there is an creased risk of thrombosis in men receiving estrogens for prostatic cancer and women for ostpartum breast engorgement. Users of oral contraceptives have an increased risk of diseases, ich as thrombophlebitis, pulmonary embolism, stroke, and myocardial infarction. Cases of retinal rombosis, mesenteric thrombosis, and optic neuritis have been reported in oral contraceptive ers An increased risk of postsurgery thromboembolic complications has also been reported in ers of oral contraceptives. If feasible, estrogen should be discontinued at least 4 weeks before rgery of the type associated with an increased risk of thromboembolism, or during periods of olonged immobilization. Estrogens should not be used in persons with active thrombophlebitis, romboembolic disorders, or in persons with a history of such disorders in association with estrogen e. They should be used with caution in patients with cerebral vascular or coronary artery disease rge doses (5 mg conjugated estrogens per day), comparable to those used to treat cancer of the ostate and breast have been shown to increase the risk of nonfatal myocardial infarction, pulmonary embolism and thrombophlebitis When doses of this size are used, any of the thromboembolic and thrombotic adverse effects should be considered a clear risk

Benign hepatic adenomas should be considered in estrogen users having abdominal pain and tenderness, abdominal mass, or hypovolemic shock Hepatocellular carcinoma has been reported in women taking estrogen-containing oral contraceptives. Increased blood pressure may occur with use of estrogens in the menopause and blood pressure should be monitored with estrogen use A worsening of glucose tolerance has been observed in patients on estrogen-containing oral contraceptives. For this reason, diabetic patients should be carefully observed Estrogens may lead to severe hypercalcemia in patients with breast cancer and bone metastases

PRECAUTIONS: Physical examination and a complete medical and family history should be taken prior to the initiation of any estrogen therapy with special reference to blood pressure, breasts, abdomen, and pelvic organs, and should include a Papanicolau smear As a general rule, estrogen should not be prescribed for longer than one year without another physical examination being performed. Conditions influenced by fluid retention such as asthma, epilepsy, migraine, and cardiac or renal dysfunction, require careful observation. Certain patients may develop manifestations of excessive estrogenic stimulation, such as abnormal or excessive uterine bleeding, mastodynia, etc. Prolonged administration of unopposed estrogen therapy has been reported to increase the risk of endometrial hyperplasia in some patients. Oral contraceptives appear to be associated with an increased incidence of mental depression Patients with a history of depression should be carefully observed. Preexisting uterine leiomyomata may increase in size during estrogen use. The pathologist should be advised of estrogen therapy when relevant specimens are submitted. If jaundice develops in any patient receiving estrogen, the medication should be discontinued while the cause is investigated Estrogens should be used with care in patients with impaired liver function, renal insufficiency, metabolic bone diseases associated with hypercalcemia, or in young patients in whom bone growth is not complete

The following changes may be expected with larger doses of estrogen:

a. Increased sulfobromophthalein retention.

b. Increased prothrombin and factors VII, VIII, IX, and X, decreased antithrombin 3, increased norepinephrine-induced platelet aggregability

c. Increased thyroid binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by PBI, T4 by column, or T4 by radioimmunoassay Free T3 resin uptake is decreased, reflecting the elevated TBG; free T4 concentration is unaltered

d. Impaired glucose tolerance

e Decreased pregnanediol excretion.

f. Reduced response to metyrapone test.

g. Reduced serum folate concentration.

h. Increased serum triglyceride and phospholipid concentration.

As a general principle, the administration of any drug to nursing mothers should be done only when clearly necessary since many drugs are excreted in human milk

ADVERSE REACTIONS: The following have been reported with estrogenic therapy, including oral contraceptives: breakthrough bleeding, spotting, change in menstrual flow; dysmenorrhea, premenstrual-like syndrome, amenorrhea during and after treatment; increase in size of uterine fibromyomata; vaginal candidiasis, change in cervical erosion and in degree of cervical secretion; cystitis-like syndrome; tenderness, enlargement, secretion (of breasts); nausea, vomiting, abdominal cramps, bloating, cholestatic jaundice; chloasma or melasma which may persist when drug is discontinued; erythema multiforme; erythema nodosum; hemorrhagic eruption; loss of scalp hair, hirsutism; steepening of corneal curvature, intolerance to contact lenses, headache, migraine, dizziness, mental depression, chorea; increase or decrease in weight; reduced carbohydrate tolerance; aggravation of porphyria; edema; changes in libido.

ACUTE OVERDOSAGE: May cause nausea, and withdrawal bleeding may occur in females.

DOSAGE AND ADMINISTRATION:

PREMARIN® Brand of Conjugated Estrogens Tablets, U.S.P.

1. *Given cyclically for short-term use only.* For treatment of moderate to severe *vasomotor* symptoms, atrophic vaginitis, or kraurosis vulvae associated with the menopause (0.3 to 1.25 mg or more daily).

The lowest dose that will control symptoms should be chosen and medication should be discontinued as promptly as possible

Administration should be cyclic (e.g., three weeks on and one week off).

Attempts to discontinue or taper medication should be made at three to six month intervals

2. *Given cyclically.* Female hypogonadism. Female castration Primary ovarian failure Osteoporosis.

Female hypogonadism 2.5 to 7.5 mg daily, in divided doses for 20 days, followed by a rest period of 10 days' duration. If bleeding does not occur by the end of this period, the same dosage schedule is repeated. The number of courses of estrogen therapy necessary to produce bleeding may vary depending on the responsiveness of the endometrium.

If bleeding occurs before the end of the 10 day period, begin a 20 day estrogen-progestin cyclic regimen with PREMARIN (Conjugated Estrogens Tablets, U.S.P.), 2.5 to 7.5 mg daily in divided doses, for 20 days During the last five days of estrogen therapy, give an oral progestin If bleeding occurs before this regimen is concluded, therapy is discontinued and may be resumed on the fifth day of bleeding

Female castration and primary ovarian failure—1.25 mg daily, cyclically. Adjust upward or downward according to response of the patient For maintenance, adjust dosage to lowest level that will provide effective control.

Osteoporosis (to retard progression)—1.25 mg daily, cyclically

3. *Given for a few days:* Prevention of postpartum breast engorgement—3.75 mg every four hours for five doses, or 1.25 mg every four hours for five days

4. *Given chronically.* Inoperable progressing prostatic cancer—1.25 to 2.5 mg three times daily.

Inoperable progressing breast cancer in appropriately selected men and postmenopausal women—10 mg three times daily for a period of at least three months.

Patients with an intact uterus should be monitored for signs of endometrial cancer and appropriate measures taken to rule out malignancy in the event of persistent or recurring abnormal vaginal bleeding

PREMARIN® Brand of Conjugated Estrogens, U.S.P. Vaginal Cream

Given cyclically for short-term use only. For treatment of atrophic vaginitis or kraurosis vulvae

The lowest dose that will control symptoms should be chosen and medication should be discontinued as promptly as possible.

Administration should be cyclic (e.g., three weeks on and one week off).

Attempts to discontinue or taper medication should be made at three to six month intervals.

Usual dosage range: 2 to 4 g daily, intravaginally or topically, depending on the severity of the condition

Treated patients with an intact uterus should be monitored closely for signs of endometrial cancer and appropriate diagnostic measures should be taken to rule out malignancy in the event of persistent or recurring abnormal vaginal bleeding

HOW SUPPLIED: PREMARIN (Conjugated Estrogens Tablets, U.S.P.). No. 865—Each *purple* tablet contains 2.5 mg in bottles of 100 and 1,000. No. 866 Each *yellow* tablet contains 1.25 mg in bottles of 100 and 1,000. Also in Cycle Pack of 21 and in unit dose package of 100. No. B64 Each *white* tablet contains 0.9 mg in bottles of 100. Also in Cycle Pack of 21. No. B67—Each *maroon* tablet contains 0.625 mg in bottles of 100 and 1,000. Also in Cycle Pack of 21 and unit dose package of 100. No. B6B—Each *green* tablet contains 0.3 mg in bottles of 100 and 1,000. The appearance of these tablets is a trademark of Ayerst Laboratories

PREMARIN (Conjugated Estrogens, U.S.P.) Vaginal Cream—No. B72—Each gram contains 0.625 mg Conjugated Estrogens, U.S.P. (Also contains cetyl esters wax, cetyl alcohol, white wax, glyceryl monostearate, propylene glycol monostearate, methyl stearate, phenylethyl alcohol, sodium lauryl sulfate, glycerin, and mineral oil.)

Combination package Each contains Net Wt. 1½ oz. (42.5 g) tube with one calibrated plastic applicator

Also Available. Refill package: Each contains Net Wt. 1½ oz (42.5 g) tube **4340/285**

References: 1. Judd HL After the menopause. *Transition* 19B3,1 19-30 **2.** Erlik Y, Tataryn IV, Meldrum DR, et al: Association of waking episodes with menopausal hot flushes *JAMA* 19B1;245 1741-1744 **3.** Meldrum DR The pathophysiology of postmenopausal symptoms *Sem Reprod Endocrinol* 19B3;1(February):11-17 **4.** Lindsay R, Hart DM, Clark DM. The minimum effective dose of estrogen for prevention of postmenopausal bone loss *Obstet Gynecol* 19B4,63 759-763 **5.** Katz WA. *Rheumatic Diseases: Diagnosis and Management* Philadelphia, JB Lippincott Co, 1977, p 672 **6.** Reese WD: A better way to screen for osteoporosis. *Contemp Ob/Gyn* 19B3,22(November):116-131.

Ayerst® AYERST LABORATORIES
New York, N.Y. 10017

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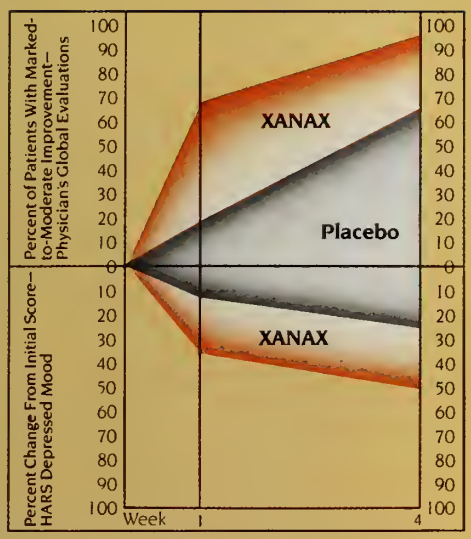
In 7 of 10
anxious
geriatrics...
Anxiety and
depressive
symptoms
go hand
in hand.

Xanax rapidly relieves anxiety with depressive symptoms.


Percent of Patients With Marked-to-Moderate Improvement—Physician's Global Evaluations
Percent Change From Initial Score—HARS Depressed Mood
100 90 80 70 60 50 40 30 20 10 0
10 20 30 40 50 60 70 80 90 100
XANAX
Placebo
XANAX
Week 1 4

In a recent clinical study[1] of 83 geriatric patients with clinical anxiety, 73% were diagnosed as having symptoms of depressed mood.

XANAX is well suited for therapy because it demonstrates greater efficacy than placebo in reducing the Hamilton Anxiety Rating Scale Total Score and individual items including depressed mood (see Figure).

With clinical advantages for geriatric patients.

- **Rapidly relieves** the symptoms of anxiety
- **Rapidly relieves** associated depressed mood
- **Well tolerated**—mild, transient drowsiness, the most commonly reported side effect the first week of therapy, shows a marked decrease thereafter and is not significantly different from that of placebo
- **Does not cause** cardiotoxicity
- **Specific geriatric dosage**—0.25 mg, two or three times daily

1 Cohn JB Double-blind safety and efficacy comparison of alprazolam and placebo in the treatment of anxiety in geriatric patients. *Curr Ther Res* 1984;35(1):100-112

Xanax® 0.25 mg Tablets
alprazolam C IV

©1984 The Upjohn Company

Upjohn THE UPJOHN COMPANY
Kalamazoo, Michigan 49001 USA

Please see next page for brief summary of prescribing information.

XANAX® Tablets
(alprazolam) C

CONTRAINDICATIONS
Patients with sensitivity to this drug or other benzodiazepines and in acute narrow angle glaucoma

WARNINGS
Not of value in psychotic patients. Caution patients against hazardous occupations requiring complete mental alertness and about the simultaneous ingestion of alcohol and other CNS depressant drugs.

Benzodiazepines can cause fetal harm in pregnant women. Warn patients of the potential hazard to the fetus. Avoid during the first trimester.

PRECAUTIONS
General: The dosage of XANAX Tablets should be reduced or withdrawn gradually, since withdrawal seizures have been reported upon abrupt withdrawal. If XANAX is combined with other psychotropics or anticonvulsant drugs, consider drug potentiation. (See Drug Interaction section.) Exercise the usual precautions regarding size of the prescription for depressed or suicidal patients. In elderly and debilitated patients, use the lowest possible dosage. (See Dosage and Administration.) Observe the usual precautions in treating patients with impaired renal or hepatic function.

Information for Patients: Alert patients about: (a) consumption of alcohol and drugs, (b) possible fetal abnormalities, (c) operating machinery or driving, (d) not increasing dose of the drug due to risk of dependence, (e) not stopping the drug abruptly. *Laboratory Tests:* Not ordinarily required in otherwise healthy patients. *Drug Interactions:* Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistamines, ethanol and other CNS depressants. Pharmacokinetic interactions with benzodiazepines have been reported. *Drug/Laboratory Test Interactions:* No consistent pattern for a specific drug or specific test. *Carcinogenesis, Mutagenesis, Impairment of Fertility:* No carcinogenic potential or impairment of fertility in rats. *Pregnancy:* See Warnings. *Nonteratogenic Effects:* The child born of a mother on benzodiazepines may be at some risk for withdrawal symptoms and neonatal flaccidity. *Labor and Delivery:* No established use. *Nursing Mothers:* Benzodiazepines are excreted in human milk. Women on XANAX should not nurse. *Pediatric Use:* Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS
Side effects are generally observed at the beginning of therapy and usually disappear with continued medication. In the usual patient, the most frequent side effects are likely to be an extension of the pharmacological activity of XANAX, e.g., drowsiness or lightheadedness.

Central nervous system: Drowsiness, lightheadedness, depression, headache, confusion, insomnia, nervousness, syncope, dizziness, akathisia, and tiredness/sleepiness.

Gastrointestinal: Dry mouth, constipation, diarrhea, nausea/vomiting, and increased salivation.

Cardiovascular: Tachycardia/palpitations, and hypotension.

Sensory: Blurred vision.

Musculoskeletal: Rigidity and tremor.

Cutaneous: Dermatitis/allergy.

Other side effects: Nasal congestion, weight gain, and weight loss.

In addition, the following adverse events have been reported with the use of anxiolytic benzodiazepines: dystonia, irritability, concentration difficulties, anorexia, loss of coordination, fatigue, sedation, slurred speech, jaundice, musculoskeletal weakness, pruritus, diplopia, dysarthria, changes in libido, menstrual irregularities, incontinence and urinary retention.

Paradoxical reactions such as stimulation, agitation, increased muscle spasticity, sleep disturbances, and hallucinations may occur. Should these occur, discontinue the drug.

During prolonged treatment, periodic blood counts, urinalysis, and blood chemistry analysis are advisable. Minor EEG changes, of unknown significance, have been observed.

DRUG ABUSE AND DEPENDENCE
Physical and Psychological Dependence: Withdrawal symptoms have occurred following abrupt discontinuance of benzodiazepines. Withdrawal seizures have occurred upon rapid decrease or abrupt discontinuation of therapy. In all patients, dosage should be gradually tapered under close supervision. Patients with a history of seizures or epilepsy should not be abruptly withdrawn from XANAX. Addiction-prone individuals should be under careful surveillance. *Controlled Substance Class:* XANAX is a controlled substance and has been assigned to schedule IV.

DOSAGE AND ADMINISTRATION
The usual starting dose is 0.25 to 0.5 mg. t.i.d. Maximum total daily dose is 4 mg. In the elderly or debilitated, the usual starting dose is 0.25 mg, two or three times daily. Reduce dosage gradually when terminating therapy, by no more than one milligram every three days.

CAUTION: FEDERAL LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION. B-3-S

Upjohn THE UPJOHN COMPANY
Kalamazoo, Michigan 49001 USA

CONTINUING MEDICAL EDUCATION

(Continued from Page 165)

April 24-26—**Clinical Advances and Research Updates in Emergency Medicine.** UCSF at Holiday Inn—Golden Gateway, San Francisco. Wednesday-Friday. 15 hrs. Fee: $300.

May 6-10—**Postgraduate Institute for Emergency Physicians, Symposium I.** UCSD at Vacation Village, San Diego. One Week. 13-16 hrs. Fee: $200-675.

May 15-19—**Wound Management Workshop.** UCSD at Holiday Inn at the Embarcadero, San Diego. Monday-Friday. 19 hrs.

May 20-24—**Topics in Emergency Medicine.** UCSF at Sheraton at Fishermans Wharf, San Francisco. Monday-Friday. 33 hrs. Fee: $400.

INTERNAL MEDICINE

February 17-22—**Advanced Problems in Infectious Diseases and Toxicology.** UCSD at Continental Inn, Aspen. Sunday-Friday. 21 hrs. Fee: $315-$430. Contact: UCSD.

February 21-24—**Federation of Societies of Neurological Science** at Hotel Intercontinental, San Diego. Thursday-Friday. 18 hrs. Contact: James Grisolia, MD, 4020 5th Ave., Ste. 404, San Diego 92138. (619) 297-1155.

February 27-March 2—**Gastroenterology Subspecialty Course.** UCSD at Town and Country Hotel, San Diego. Wednesday-Saturday. 12 hrs.

March 8-10—**Frontiers of Rheumatology.** Annenberg Center for Health Science, Rancho Mirage. Friday-Sunday. Contact: Eisenhower Medical Center, 39000 Bob Hope Dr., Rancho Mirage, CA 92270.

March 13-16—**Office Endocrinology: 1985.** UCSF at Granlibakken Ski and Raquet Resort, Tahoe City. Wednesday-Saturday.

March 15-16—**Reider Laser Symposium in Urology.** UCI. Friday-Saturday. 14 hrs.

March 18—**Reider Laser Symposium in Gastroenterology.** UCI. Monday. 7 hrs.

March 18-19—**Reider Laser Symposium in Neurosurgery.** UCI. Monday-Tuesday. 12 hrs.

March 18-20—**Gastroenterology Course.** UCSF at Yosemite. Monday-Wednesday. Contact: UCSF.

March 19-22—**Internal Medicine Update.** UCD at Red Lion Motor Inn, Sacramento. Tuesday-Friday.

March 23—**Reider Laser Symposium in Head, Neck, and Facial Surgery.** UCI. Saturday. 7 hrs.

April 12-13—**Update in Gastroenterology.** Annenberg Center for Health Sciences, at Rancho Mirage. Friday-Saturday. Contact: Annenberg Center for

(Continued on Page 180)

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(Continued from Page 176)

Health Sciences, Eisenhower Medical Center, 39000 Bob Hope Dr., Rancho Mirage 92270. (800) 621-7322.

April 22-24—**Advances in Infectious Diseases.** UCSF at Mark Hopkins Hotel, San Francisco. Monday-Wednesday. Fee: $325.

April 24—**Thyroid '85.** The Hospital of the Good Samaritan at Hyatt Regency Hotel, Los Angeles. Wednesday. 6 hrs. Contact: Dolores Gay, 616 South Witmer St., Los Angeles 90017. (213) 977-2352.

April 27—**Nephrology.** UCSF at Fresno. Saturday.

May 8—**Gastroenterology: G.I. Bleeding.** LLU. Wednesday. 4 hrs.

May 13-17—**Advances in Internal Medicine.** UCSF. Wednesday-Sunday. Fee: $465.

May 17-18—**Clinical Concerns in Hemodialysis Therapy.** Rutgers Medical School at Sheraton Harbor Island West Hotel, San Diego. Friday-Saturday. 11.5 hrs. Contact: Richard A. Sherman, MD, Academic Health Science Center, UMDNJ-Rutgers Medical School, CN-19, New Brunswick, NJ 08903.

OBSTETRICS AND GYNECOLOGY

February 16-23—**Perinatal Medicine.** USC at Royal Lahaina, Maui, HI. One week.

February 23—**OB/GYN.** UCSF at Fresno. Saturday. Contact: UCSF.

March 2-9—**6th Annual Symposium on Current Topics in Obstetrics.** UCI at Aspen, Colorado. One week. 23 hrs. Contact: UCI.

March 7-10—**Recent Advances in OB/GYN: 8th Annual.** UCSD at Hotel Intercontinental, San Diego. Thursday-Saturday. 21 hrs.

March 15-16—**30th Annual T. Hart Baker, MD Symposium.** Southern California Kaiser Permanente at Hyatt Regency Hotel, Long Beach. Friday-Saturday. Contact: Southern California Kaiser Permanente, 4747 Sunset Blvd, Los Angeles 90027.

March 15-16—**Reider Laser Symposium in Gynecology.** UCI. Friday-Saturday. 11 hrs.

March 16-17—**Uses of Real-time Ultrasound in Gynecology and Infertility.** UCI at Hotel Inter-Continental, San Diego. Saturday-Sunday. 16 hrs.

March 21-24—**Changing Practice of Obstetrical Anesthesiology and High Risk Pregnancy.** UCSF at Hotel Meridien, San Francisco. Thursday-Sunday. 16 hrs.

March 22-24—**Gynecology Surgery with Emphasis on Gynecologic Urology.** UCI at The Palm Springs Marquis, Palm Springs. Friday-Sunday. 15 hrs.

March 27-30—**Horizons in Reproductive Health.** Planned Parenthood and UCSD at Hotel Del Coronado, San Diego. Wednesday-Saturday. 15.5 hrs. Contact: Nomi Feldman, Conference Coord., 3770 Tansy, San Diego 92121. (619) 453-6222.

April 20—**Infertility Update III.** Scripps Clinic and Research Foundation at La Jolla. Saturday. Contact: Scripps Clinic and Research Foundation, 10666 N. Torrey Pines Rd, La Jolla 92037. (619) 455-9100.

OPHTHALMOLOGY

March 1-2—**14th Jules Stein Seminar: Retino Vitreal.** Jules Stein Eye Institute at Century Plaza Hotel, Los Angeles. 16 hrs. Contact: JSEI, UCLA School of Medicine, Los Angeles 90024. (213) 825-4617.

March 9—**Ophthalmology Residents and Fellows Day.** JSFI at Los Angeles. Saturday. 5 hrs. Fee: $15 Non-members. Contact: Lu Hendricks, JSEI, 800 Westwood Plaza, Los Angeles 90024. (213) 825-4617.

March 14-15—**Modern Surgical Techniques and Their Effects of the Cornea.** Pacific Medical Center at Clift Hotel, San Francisco. Thursday-Friday. Contact: Pacific Medical Center, Continuing Education, PO Box 7999, San Francisco 94120. (415) 563-4321, ext. 2761.

March 21-22—**Reider Laser Symposium in Ophthalmology.** UCI. Thursday-Friday. 13 hrs.

April 12-13—**16th Jules Stein Lecture and Annual Postgraduate Seminar.** JSEI. Saturday-Sunday. 16 hrs. Fee: $375. Contact: Lu Hendricks, Jules Stein Eye Institute, 800 Westwood Plaza, Los Angeles 90024. (213) 825-4617.

May 18—**Neodymium—YAG Laser Course.** Jules Stein Eye Institute at Los Angeles. Saturday. 8 hrs. Fee: $200. Contact: Lu Hendricks, JSEI, 800 Westwood Plaza, Los Angeles 90024. (213) 825-4617.

PATHOLOGY

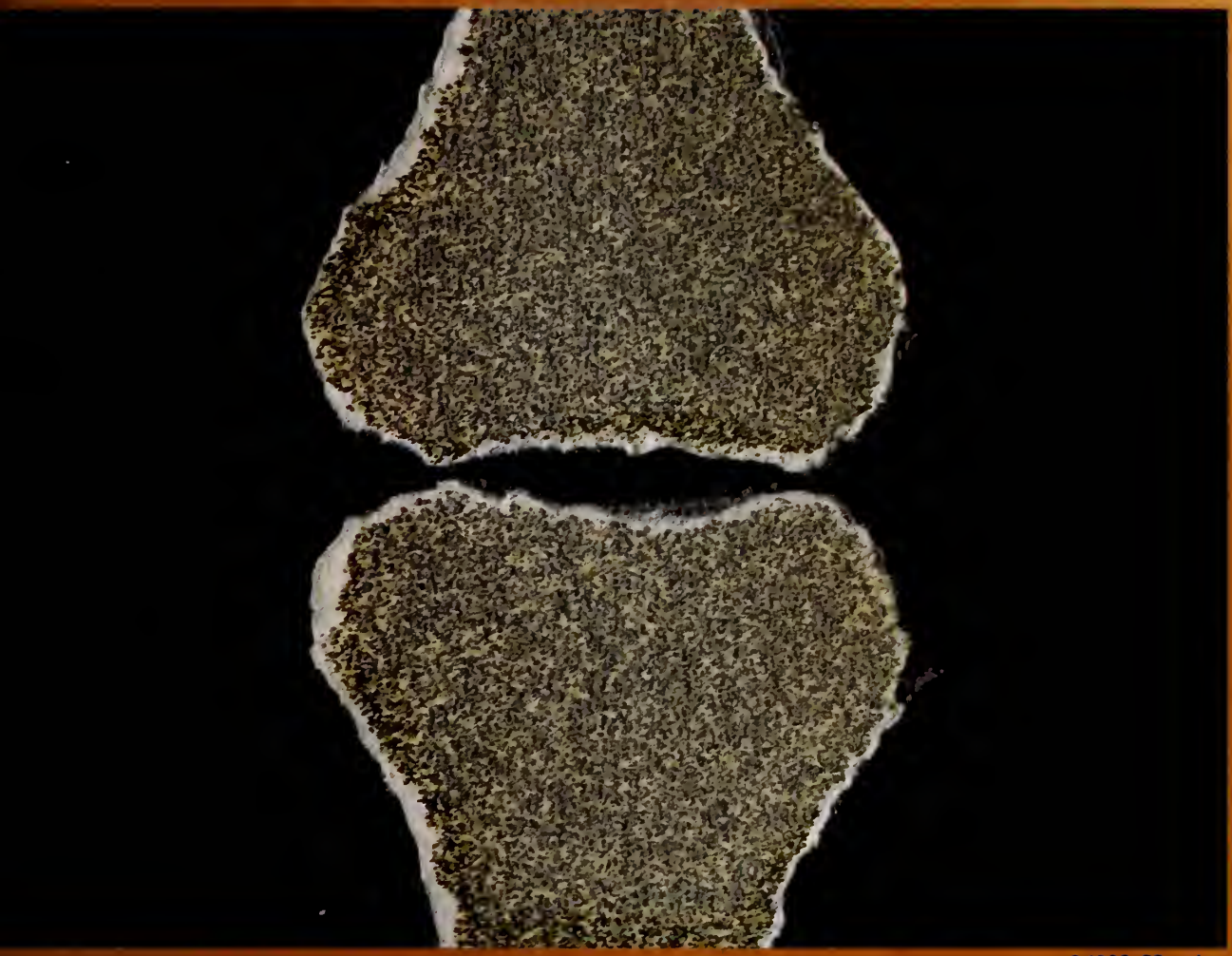
February 16—**Oxygen Radicals, Pathology and Aging.** UCSD at Holiday Inn at the Embarcadero, San Diego. Saturday.

May 23-24—**Symposium on Current Issues in Anatomic Pathology.** UCSF. Thursday-Friday.

PEDIATRICS

March 7-9—**Brain Insults in Infants and Children: Pathology, Evaluation, Diagnosis and Acute Management.** UCSD at Holiday Inn Embarcadero, San Diego. 17 hrs. Contact: UCSD.

(Continued on Page 192)



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This is how an arthritis patient's joints often feel.

You can help these patients feel better with one-a-day FELDENE (piroxicam).
Four good reasons:

- It's effective—proven relief of the pain and inflammation of rheumatoid arthritis and osteoarthritis in millions of patients, in 80 countries all around the world.
- It's efficient—once daily, 20-mg dose provides round-the-clock relief, improves compliance and remains effective during long-term therapy, maintaining 24-hour therapeutic blood levels once steady state is reached in 7 to 12 days.

Feldene® *(PIROXICAM)* *20 mg capsules*

ONE-A-DAY

Please see FELDENE (piroxicam) prescribing information on the following page.

Feldene®
(PIROXICAM) 20 mg capsules

20 mg once-a-day for initiation and maintenance

Prescribing Information

FELDENE® (piroxicam) Capsules *For Oral Use*

DESCRIPTION FELDENE (piroxicam) is 4-Hydroxy-2-methyl-*N*-2-pyridinyl-2*H*-1,2-benzothiazine-3-carboxamide 1,1-dioxide, an oxicam. Members of the oxicam family are not carboxylic acids, but they are acidic by virtue of the enolic 4-hydroxy substituent. FELDENE occurs as a white crystalline solid, sparingly soluble in water, dilute acid and most organic solvents. It is slightly soluble in alcohols and in aqueous alkaline solution. It exhibits e weakly acidic 4-hydroxy proton (pKa 5.1) and a weekly basic pyridyl nitrogen (pKa 1.8).

CLINICAL PHARMACOLOGY FELDENE has shown anti-inflammatory, analgesic and antipyretic properties in animals. Edema, erythema, tissue proliferation, fever, and pain can alf be inhibited in laboratory animals by the administration of FELDENE. It is effective regardless of the etiology of the inflammation. The mode of action of FELDENE is not fully established at this time. However, a common mechanism for the above effects may exist in the ability of FELDENE to inhibit the biosynthesis of prostaglandins, known mediators of inflammation.

It is established that FELDENE does not act by stimulating the pituitary-adrenal axis

FELDENE is well absorbed following oral administration. Drug plasme concentrations are proportional tor 10 and 20 mg doses, generally paak within three to tive hours after medication, and subsequently decline with a mean half-life of 50 hours (range of 30 to 86 hours, although values outside of this range have been encountered).

This prolonged half-life results in the maintenance of relatively stable plasma concentrations throughout the day on once daily doses and to significant drug accumulation upon multiple dosing. A single 20 mg dose generally produces peak piroxicam plasma levels of 1.5 to 2 mcg/ml, while maximum drug plasma concentretions, efter repeeted daily ingestion of 20 mg FELDENE, usually stabilize at 3-8 mcg/ml. Most patients approximate steady state plasma levels within 7 to 12 days. Higher levels, which epproximate steady state at two to three weeks, have been observed in patients in whom longer plasma half-lives of piroxicam occurred.

FELDENE and its biotrensformation products ere excreted in urine and feces, with about twice es much appeering in the urine as the feces. Metabolism occurs by hydroxylation at the 5 position of the pyridyl side chain and conjugetion of this product; by cyclodehydration; end by a sequence of reactions involving hydrolysis of the amide linkage, decerboxyletion, ring contraction, and N-demethylation. Less than 5% of the daily dose is excreted unchanged.

Concurrent administration of aspirin (3900 mg/day) and FELDENE (20 mg day), resulted in a reduction of plasma levels of piroxicam to ebout 80% of their normal values. The use of FELDENE in conjunction with aspinn is not recommended because deta are inadequate to demonatrate that the combination produces greater improvement then that achieved with espirin alone and the potentiel for adverse reactions is increased. Concomitant administration of antacids hed no effect on FELDENE plasma levels. The effects of impaired renal function or hepatic disease on plasma levels have not been established.

FELDENE, like salicylates end other nonsteroidel anti-inflemmatory agents, is essociated with symptoms of gastrointestinal tract irritation (see ADVERSE REACTIONS). However, in a study utilizing ^{51}Cr-tagged red blood cells, 20 mg of FELDENE administered as e single dose tor tour days did not result in a significant increase in fecel blood loss end did not detectably affect the gastric mucosa. In the same study a total daily dose of 3900 mg of aspirin, i.e., 972 mg q.i.d., caused a significant increase in fecal blood toss and mucosal lesions as demonstreted by gestroscopy.

In controlled clinical trials, the effectiveness of FELDENE has been established tor both acute exacerbations end long-term management of rheumatoid arthritis and osteoarthritis.

The therapeutic effects of FELDENE are evident early in the treatment of both diseases with a progressive increase in response over several (8-12) weeks. Efficacy is seen in terms of pain relief and, when present, subsidence of inflammation.

Doses of 20 mg/day FELDENE displey a therapeutic effect comparable to therapeutic doses of aspirin, with a lower incidence of minor gastrointestinal effects and tinnitus.

FELDENE has been administered concomitantly with fixed doses of gold and corticosteroids. The existence of a "steroid-sparing" effect hes not been adequately studied to date.

INDICATIONS AND USAGE FELDENE is indicated tor acute or long-term use in the relief of signs and symptoms of the following:

1. osteoarthritis
2. rheumatoid arthritis

Dosage recommendations for use in children have not been established.

CONTRAINDICATIONS FELDENE should not be used in patients who have previously exhibited hypersensitivity to it, or in individuals with the syndrome comprised of bronchospesm, nesel polyps, and angioedeme precipitated by aspirin or other nonsteroidal anti-inflemmatory drugs.

WARNINGS Peptic ulceration, perforation, and G I bleeding—sometimes severe, and, in some instances fetal—have been reported with patients receiving FELDENE. If FELDENE must be given to patients with a history of upper gestrointestinal tract disease, the petient should be under close supervision (see ADVERSE REACTIONS). In controlled clinicel trials, incidence of peptic ulceration with the maximum recommended FELDENE capsule dose of 20 mg per dey wes 0.8%. The use of doses higher than the recommended dose is associeted with an increase in the incidence of gastrointestinal irritation end ulcers.

PRECAUTIONS As with other anti-inflammatory agents, long-term edministration to enimals results in renal papillary necrosis and related pethology in rats, mice, and dogs.

Acute renal feilure end hyparkalemia as well as reversible elevations of BUN and serum creatinine have been reported with FELDENE. The effect is thought to result from inhibition of renal prostaglandin synthesis resulting in e change in medullery and deep cortical blood flow with en attendent effect on renal tunction. Patients with impaired renal function and on diuretics es well es elderly patients who have decreased renal function are more at nsk. Because of the extensive renel excretion of piroxicam and its biotransformation products (less than 5% of the daily dose excreted unchanged, see CLINICAL PHARMACOLOGY), lower doses of piroxicam should be anticipated in patients with impaired renal function and they should be carefully monitored. In addition to reversible changes in renal function, interstitial nephritis, glomerulitis, papillary necrosis and the nephrotic syndrome have been reported with FELDENE.

Although other nonsteroidel enti-inflammatory drugs do not have the same direct effects on platelets that espirin does, all drugs inhibiting prostaglandin biosynthesis do interfere with platelet function to some degree, therefore, patients who mey be adversely effected by such an action should be carefully observed when FELDENE is administered.

Because of reports of adverse eye findings with nonsteroidal enti-inflammatory agents, it is recommended thet patients who develop visuel compleints during treetment with FELDENE heve ophthalmic evaluation.

As with other nonsteroidal anti-inffammetory drugs, bordertine elevations of one or more liver tests may occur in up to 15% of patients. These abnormelities may progress, may remain essentially unchanged, or may be transient with continued therapy. The SGPT (ALT) test is probably the most sensitive indicetor of liver dysfunction. Meeningful (3 times the upper limit of normal) elevations of SGPT or SGOT (AST) occurred in controlled clinical trials in less than 1% of patients. A patient with symptoms end or signs suggesting liver dysfunction, or in whom an ebnormal liver test has occurred, should be eveluated tor evidence of the development of more severe hepatic reaction while on therapy with FELDENE. Severe hepatic reactions, including jaundice and cases of fatal hepatitis, have been reported with FELDENE. Although such reactions ere rare, if ebnormal liver tests persist or worsen, if clinical signs end symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g. eosinophilie, rash, etc.), FELDENE should be discontinued. (See also ADVERSE REACTIONS.)

Although et the recommended dose of 20 mg day of FELDENE increased fecel blood loss due to gastrointestinel irritation did not occur (see CLINICAL PHARMACOLOGY), in about 4% of the patients treeted with FELDENE alone or concomitantly with aspirin, reductions in hemoglobin end hemetocrit velues were observed. Therefore, these values should be determined if signs or symptoms of anemie occur.

Peripheral edeme has been observed in approximetely 2% of the patients treated with FELDENE. Therefore, as with other nonsteroidal enti-inflammatory drugs, FELDENE should be used with ceution in patients with heart failure, hypertension or other conditions predisposing to fluid retention, since its usage mey be associated with e worsening of these conditions.

A combination of dermatological and/or ellergic signs and symptoms suggestive of serum sickness have occasionally occurred in conjunction with the use of FELDENE. These include arthralgias, pruritus, fever, fetigue, and rash including vesiculo bullous reactions and exfoliative dermatitis.

DRUG INTERACTIONS FELDENE is highly protein bound, and, therefore, might be expected to displace other protein-bound drugs. Although this has not occurred in *in vitro* studies with coumann-type anticoagulants, interactions with coumerin-typa anticoagulants have been reported with FELDENE since merketing. therefore, physicians should closely monitor patients for e change in dosage requirements when administering FELDENE (piroxicam) to patients on coumarin-type anticoagulants and other highly protein-bound drugs.

Plasma levels of piroxicam are depressed to approximately 80% of their normal values when FELDENE (piroxicem) is administered in conjunction with aspinn (3900 mg/day), but concomitant administration of antacids has no effect on piroxicam plasma levels (see CLINICAL PHARMACOLOGY).

Nonsteroidal anti-inflammatory agents, including FELDENE, have been reported to increase steedy state plasma lithium levels. It is recommended that plasma lithium levels be monitored when initiating, adjusting and discontinuing FELDENE.

Carcinogenesis, Chronic Animal Toxicity and Impairment of Fertility Subacute and chronic toxicity studies have been carned out in rats, mice, dogs, and monkeys.

The pethology most often aeen wes that characteristically associeted with the animal toxicology of anti-inflammatory agents: renal papillary necrosis (see PRECAUTIONS) end gastrointestinal lesions.

In classicel studies in laboratory animals piroxicam did not show any teretogenic potential. Reproductive studies revealed no impairment of fertility in animals.

Pregnancy and Nursing Mothers Like other drugs which inhibit the synthesis and release of prostaglandins, piroxicam increased the incidence of dystocie and delayed partuntion in pregnant animals when piroxicam administration was continued late into pregnancy. Gastrointestinal tract toxicity was increased in pregnent females in the last trimester of pregnancy compared to nonpregnant females or females in earlier trimesters of pregnancy.

FELDENE is not recommended for use in nursing mothers or in pregnent women because of the animel findings and since safety for such use has not been established in humans.

Use in Children Dosage recommendations and indications for use in children have not been established.

ADVERSE REACTIONS The incidence of edverse reactions to piroxicam is based on clinical trials involving approximately 2300 patients, about 400 of whom were treated for more than one yeer and 170 for more then two yeers. About 30% of alt patients receiving deily doses of 20 mg FELDENE experienced side effects. Gastrointeatinel symptoms were the most prominent side effects—occurring in epproximetely 20% of the patients, which in most instences did not interfere with the course of therapy. Of the patients experiencing gestrointestinal side effects, approximately 5% discontinued therapy with an overall incidence of peptic ulceration of about 1%.

Other than the gastrointestinel symptoms, edema, dizziness, headache, changes in hematological parameters, and resh heve been reported in a small percentage of patients. Routine ophthalmoscopy end slit-lamp examinations have revealed no evidence of ocular changes in 205 petients followed from 3 to 24 months while on therapy.

Incidence Greater Than 1% The following adverse reactions occurred more frequently than 1 in 100.

Gastrointestinal: stomatitis, anorexia, epigastric distress*, nausea*, constipation, abdominal discomfort, flatulence, diarrhee, abdominal pain, indigestion

Hemetological: decreases in hemoglobin* and hematocrit* (see PRECAUTIONS), anemia, leucopenia, eosinophilie

Dermatologic: pruritus, rash

Central Nervous System: dizziness, somnolence, vertigo

Urogenitel: BUN and creatinine elevations (see PRECAUTIONS)

Body as e Whole: headeche, maleise

Speciel Senses: tinnitus

Cardiovascular/Respiratory: edema (see PRECAUTIONS)

*Reactions occurring in 3% to 9% of patients treated with FELDENE. Reactions occurring in 1% of patients are unmarked.

Incidence Less Than 1% (Causal Relationship Probable)

The following adverse reactions occurred less frequently than 1 in 100. The probability exists that there is e causal reletionship between FELDENE and these reactions.

Gastrointestinal: liver function ebnormalities, jaundice, hepatitis (see PRECAUTIONS), vomiting, hematemesis, melena, gestrointestinel bleeding, perforetion and ulceration (see WARNINGS), dry mouth

Hemetological: thrombocytopenia, patechial resh, ecchymosis, bone merrow depression including aplastic anemie, epiatexis

Dermatologic: sweeting, erytheme, bruising, desquametion, exfolietive dermatitis, erythema multiforme, toxic epidermal necrolysis, Stevens-Johnson syndrome, vesiculo bullous reaction, photoallergic skin reactiona

Central Nervous System: depression, insomnia, nervousness

Urogenital: hematuria, proteinuria, interstitiel nephritis, renel failure, hyperkalemia, glomerulitis, papillary necrosis, nephrotic syndrome (see PRECAUTIONS)

Body as a Whole: pain (colic), fever, flu-like syndrome (see PRECAUTIONS)

Speciel Sensas: swollen eyes, blurred vision, eye irritations

Cardiovascular/Respiratory: hypertension, worsening of congestive heart failure (see PRECAUTIONS), exacerbation of engine

Metebolic: hypoglycemia, hyperglycemia, weight increase, weight decrease

Hypersensitivity: enephylaxis, bronchospasm, urticaria/engioedema, vasculitis, "serum sickness" (see PRECAUTIONS)

Incidence Less Than 1% (Ceusal Relationship Unknown)

Other edverse reactions were reported with a frequency of less than 1 in 100 but a causal relationship between FELDENE end the reaction could not be determined.

Gastrointestinal: pancreatitis

Dermatologic: onycholysis, loss of heir

Central Nervous System: akathisie, hallucinations, mood alterations, dream abnormalities, mental confusion, paresthesias

Urogenitel System: dysurie

Body as a Whole: weakness

Cardiovescular Respiretory: palpitetions, dyspnea

Hypersensitivity: positive ANA

OVERDOSAGE: In the event treatment for overdosage is required, the long plasma half-life (see CLINICAL PHARMACOLOGY) of piroxicam should be considered. The absence of experience with acute overdosage precludes characterization of sequelae and recommendation of specific antidotal efficacy at this time. It is reesonable to assume, however, that the standard measures of gastric evacuation and generel supportive therapy would apply. In eddition to supportive measures, the use of activated charcoal may effectively reduce the absorption and reebsorption of piroxicem. Experiments in dogs have demonstrated that the use of multiple-dose treatments with activated charcoal could reduce the half-life of piroxicem elimination from 27 hours (without charcoal) to 11 hours and reduce the systemic bioavellebility of piroxicam by as much as 37% when activated charcoal is given es late as 6 hours after administration of piroxicem.

ADMINISTRATION AND DOSAGE Rheumatoid Arthritis, Osteoarthritis It is recommended that FELDENE therapy be initiated end maintained at a single daily dose of 20 mg. If desired the daily dose may be divided. Because of the long half-life of FELDENE, steady state blood levels ere not reeched for 7-12 deys. Therefore although the therapeutic effects of FELDENE em evident early in treatment, there is a progressive increese in response over several weeks and the effect of therapy should not be essessed for two weeks.

Dosage recommendations and indications for use in children have not been established.

HOW SUPPLIED FELDENE Capsules for orel administration

Bottles of 100: 10 mg (NDC 0663-3220-68) maroon and blue #322
20 mg (NDC 0663-3230-66) maroon #323

Bottles of 500: 20 mg (NDC 0663-3230-73) maroon #323

Unit dose packages of 100: 20 mg (NDC 0663-3230-41) maroon #323

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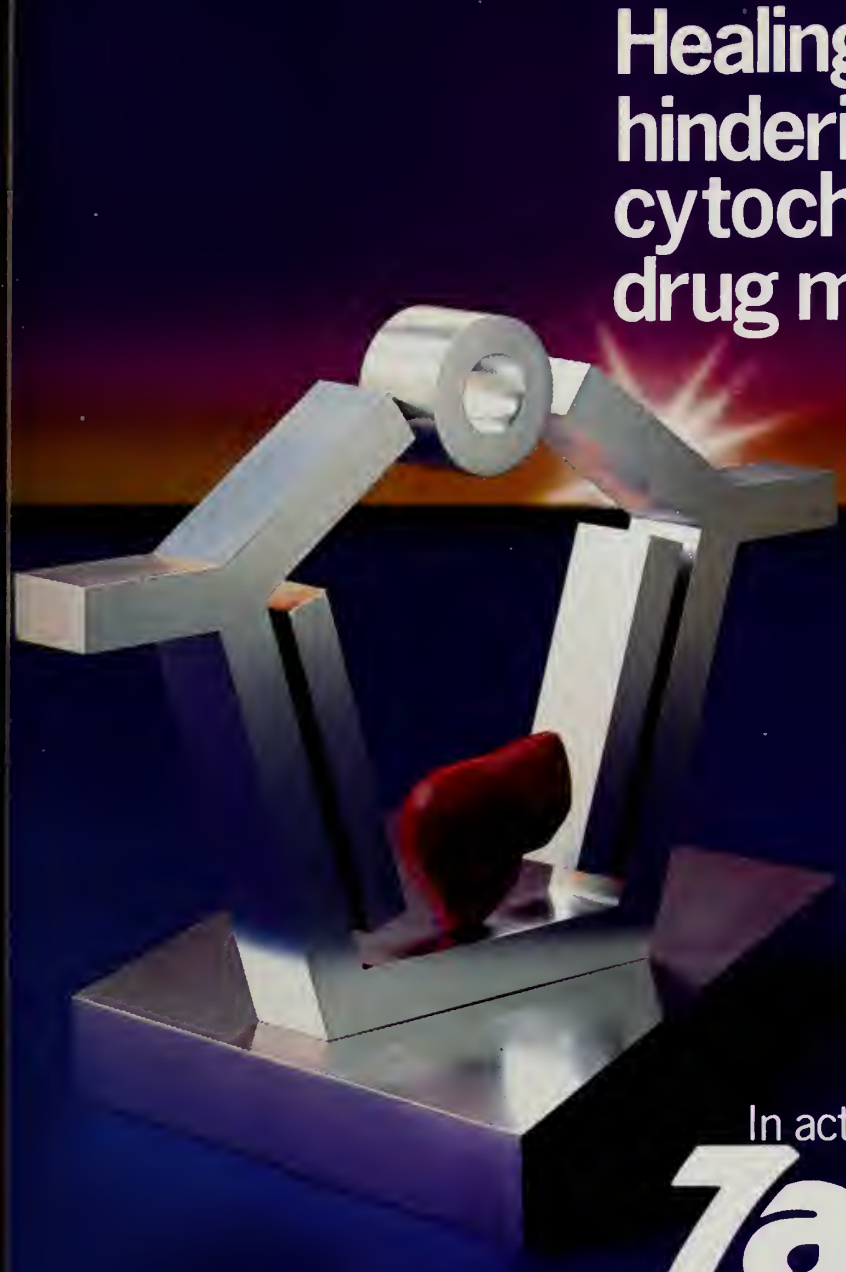
Pfizer

LABORATORIES DIVISION

PFIZER INC

Healing, without hindering hepatic cytochrome P-450 drug metabolism



In active duodenal ulcer

Zantac®

[ranitidine HCl/Glaxo] 150mg tablets

Selective inhibition

Theophylline...warfarin...phenytoin. All metabolized by the hepatic cytochrome P-450 system—all potentially interactive with cimetidine. Zantac provides effective healing of duodenal ulcers without significant interference with the hepatic cytochrome P-450 enzyme system. So Zantac may be administered concomitantly with these commonly used drugs without fear of a clinically significant interaction.

Glaxo ROCHE

ase see next page for Brief Summary.

In active duodenal ulcer

Zantac®

[ranitidine HCl/Glaxo] 150mg tablets

Selective inhibition

BRIEF SUMMARY OF PRESCRIBING INFORMATION

INDICATIONS AND USAGE: ZANTAC® (ranitidine hydrochloride) is indicated in:

1. Short-term treatment of active duodenal ulcer. Most patients heal within 4 weeks. Studies available to date have not assessed the safety of ranitidine in uncomplicated duodenal ulcer for periods of more than 8 weeks.
2. The treatment of pathological hypersecretory conditions (eg, Zollinger-Ellison Syndrome and systemic mastocytosis).

In active duodenal ulcer and hypersecretory states, antacids should be given as needed for relief of pain.

CONTRAINDICATIONS: ZANTAC® is contraindicated for patients known to have hypersensitivity to the drug.

PRECAUTIONS: General: 1. Symptomatic response to ZANTAC® therapy does not preclude the presence of gastric malignancy. 2. Since ZANTAC is excreted primarily by the kidney, dosage should be adjusted in patients with impaired renal function (see DOSAGE AND ADMINISTRATION). Caution should be observed in patients with hepatic dysfunction; ZANTAC is metabolized in the liver and, at present, the effects of hepatic disease on the metabolism of ZANTAC is unknown.

Laboratory Tests: False positive tests for urine protein with Multistix® may occur during ZANTAC therapy and therefore testing with sulphosalicylic acid is recommended.

Drug Interactions: Although ZANTAC has been reported to bind weakly to cytochrome P450 *in vitro*, recommended doses of the drug do not inhibit the action of the cytochrome P450-linked oxygenase enzymes in the liver. However, there have been isolated reports of drug interactions which suggest that ZANTAC may affect the bioavailability of certain drugs by some mechanism as yet unidentified (eg, a pH dependent effect on absorption or a change in volume of distribution).

Carcinogenesis, Mutagenesis, and Impairment of Fertility: There was no indication of tumorigenic or carcinogenic effects in lifespan studies in mice and rats at doses up to 2000 mg/kg/day.

Ranitidine was not mutagenic in standard bacterial tests *(Salmonella, E. Coli)* for mutagenicity at concentrations up to the maximum recommended for these assays.

In a dominant lethal assay a single oral dose of 1000 mg/kg to male rats was without effect on the outcome of 2 matings per week for the next 9 weeks.

Usage in Pregnancy: ***Pregnancy Category B.*** Reproduction studies have been performed in rats and rabbits at doses up to 160 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to ZANTAC (ranitidine hydrochloride). There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: ZANTAC is secreted in human milk. Caution should be exercised when ZANTAC is administered to a nursing mother.

Pediatric Use: Safety and effectiveness in children have not been established.

Use in Elderly Patients: Ulcer healing rates in elderly patients (65-82 years) were no different from those in younger age groups. The incidence rates for adverse events and laboratory abnormalities were also not different from those seen in other age groups.

ADVERSE REACTIONS: The following have been reported as events in clinical trials or in the routine management of patients treated with ZANTAC.® The relationship to ZANTAC therapy has been unclear in many cases. Headache, sometimes severe, seems to be related to ZANTAC administration.

Central Nervous System: Rarely, malaise, dizziness, somnolence, insomnia and vertigo. Rare cases of reversible mental confusion, agitation, depression and hallucinations have been reported, predominantly in severely ill elderly patients.

Cardiovascular: Rare reports of tachycardia, bradycardia, premature ventricular beats.

Gastrointestinal: Constipation, diarrhea, nausea/vomiting, abdominal discomfort/pain.

Hepatic: In normal volunteers, SGPT values were increased to at least twice the pre-treatment levels in 6 of 12 subjects receiving 100 mg q.i.d. IV for 7 days, and in 4 of 24 subjects receiving 50 q.i.d. IV for 5 days. With oral administration there have been occasional reports of reversible hepatitis, hepatocellular or hepatocanalicular or mixed, with or without jaundice.

Musculoskeletal: Rare reports of arthralgias.

Hematologic: Rare reports of reversible leukopenia, granulocytopenia, thrombocytopenia and pancytopenia.

Endocrine: Controlled studies in animals and man have shown no stimulation of any pituitary hormone by ZANTAC, no anti-androgenic activity, and cimetidine-induced gynecomastia and impotence in hypersecretory patients have resolved when ZANTAC (ranitidine hydrochloride) was substituted. However, occasional cases of gynecomastia, impotence and loss of libido have been reported in male patients receiving ZANTAC, but the incidence did not differ from that in the general population.

Integumental: Rash and rarely alopecia.

Other: Rare cases of hypersensitivity reactions (eg, bronchospasm, fever, rash, eosinophilia), small increases in serum creatinine.

OVERDOSAGE: There is no experience to date with deliberate overdosage. The usual measures to remove unabsorbed material from the gastrointestinal tract, clinical monitoring and supportive therapy should be employed.

Studies in dogs receiving doses of ZANTAC® in excess of 225 mg/day have shown muscular tremors, vomiting, and rapid respiration. Single oral doses of 1000 mg/kg in mice and rats were not lethal. Intravenous LD_{50} values in rat and mouse were 83 mg/kg and 77 mg/kg, respectively.

DOSAGE AND ADMINISTRATION: Dosage Adjustment for Patients with Impaired Renal Function: On the basis of experience with a group of subjects with severely impaired renal function treated with ZANTAC, the recommended dose in patients with a creatinine clearance less than 50 ml/min is 150 mg every 24 hours. Should the patient's condition require, the frequency of dosing may be increased to every 12 hours or even further with caution. Hemodialysis reduces the level of circulating ranitidine. Ideally, the dosage schedule should be adjusted so that the timing of a scheduled dose coincides with the end of hemodialysis.

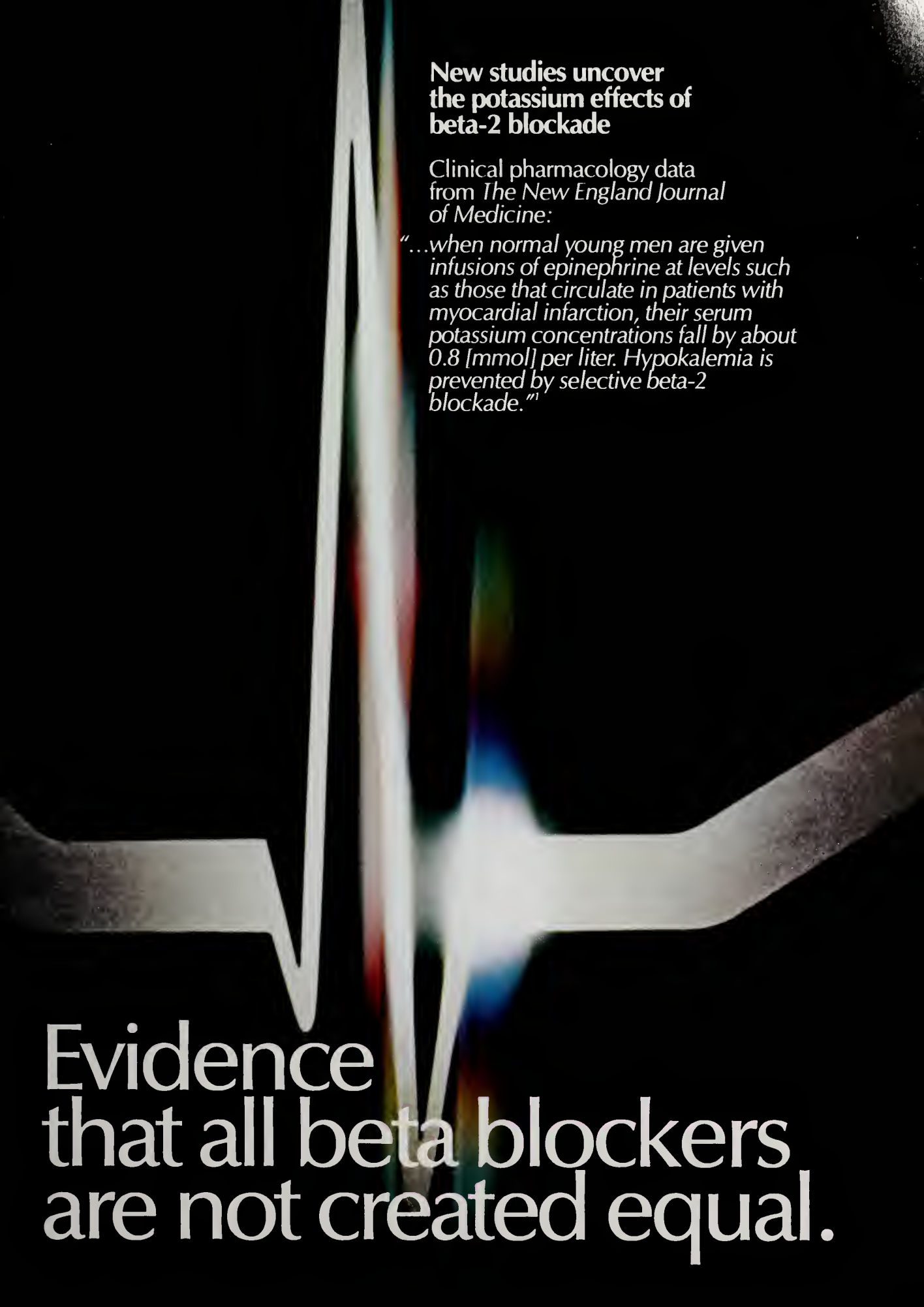
HOW SUPPLIED: ZANTAC® Tablets (ranitidine hydrochloride equivalent to 150 mg ranitidine) are white tablets embossed with "ZANTAC 15" on one side and "Glaxo" on the other. They are available in bottles of 30 tablets (NDC 0173-0344-40), 60 tablets (NDC 0173-0344-42) and unit dose packs of 100 tablets (NDC 0173-0344-47).

Store at controlled room temperature in a dry place. Protect from light. Replace cap securely after each opening.

Glaxo Inc., Research Triangle Park, NC 27709 Revised: July

Glaxo

Glaxo Inc., Research Triangle Park, NC 27709



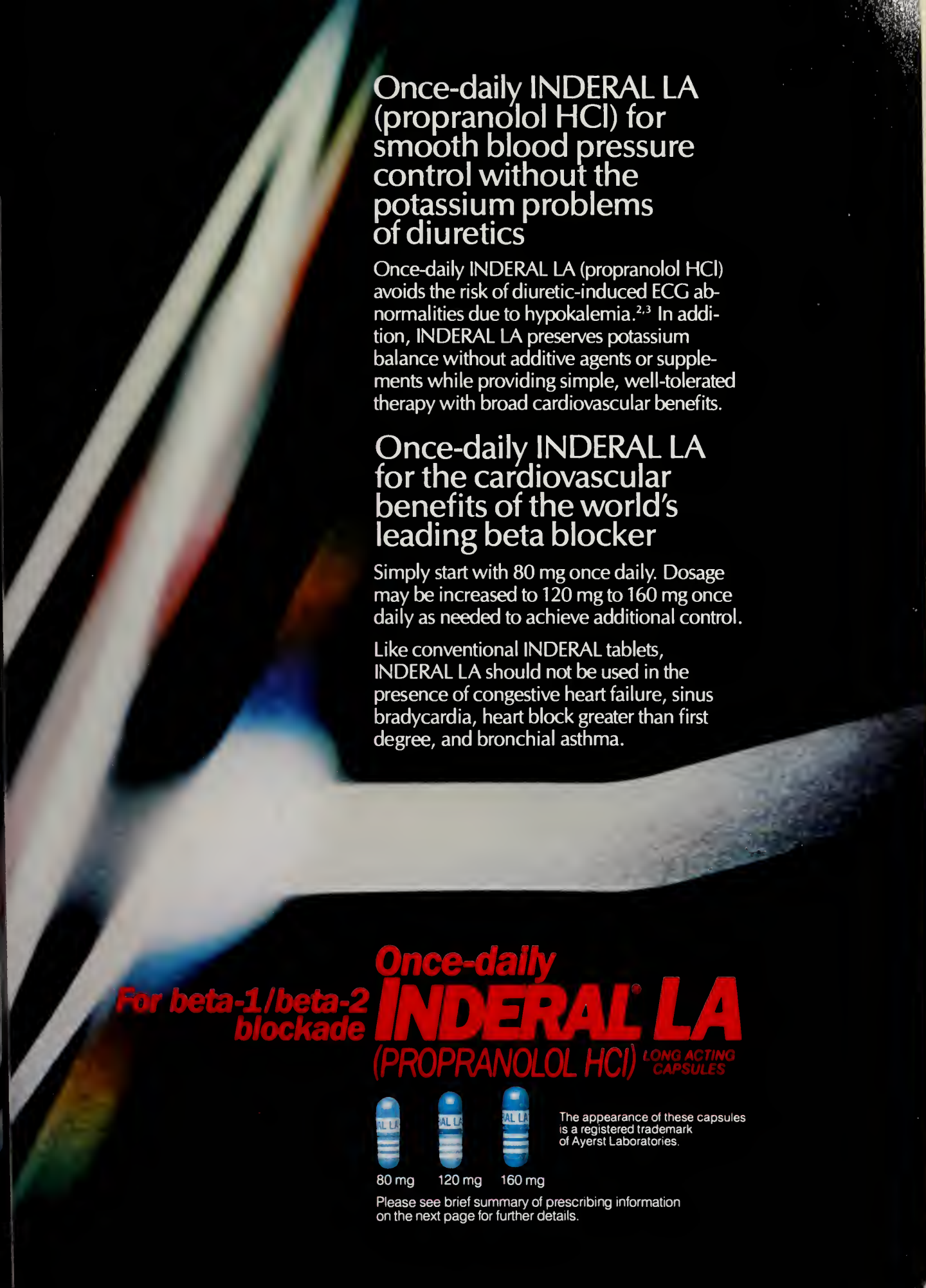
New studies uncover the potassium effects of beta-2 blockade

Clinical pharmacology data from *The New England Journal of Medicine:*

"...when normal young men are given infusions of epinephrine at levels such as those that circulate in patients with myocardial infarction, their serum potassium concentrations fall by about 0.8 [mmol] per liter. Hypokalemia is prevented by selective beta-2 blockade."[1]

Evidence that all beta blockers are not created equal.

Right from the start in hypertension...



Once-daily INDERAL LA (propranolol HCl) for smooth blood pressure control without the potassium problems of diuretics

Once-daily INDERAL LA (propranolol HCl) avoids the risk of diuretic-induced ECG abnormalities due to hypokalemia.[2,3] In addition, INDERAL LA preserves potassium balance without additive agents or supplements while providing simple, well-tolerated therapy with broad cardiovascular benefits.

Once-daily INDERAL LA for the cardiovascular benefits of the world's leading beta blocker

Simply start with 80 mg once daily. Dosage may be increased to 120 mg to 160 mg once daily as needed to achieve additional control.

Like conventional INDERAL tablets, INDERAL LA should not be used in the presence of congestive heart failure, sinus bradycardia, heart block greater than first degree, and bronchial asthma.

For beta-1/beta-2 blockade

Once-daily INDERAL® LA

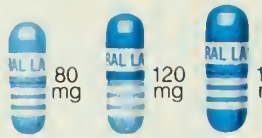
(PROPRANOLOL HCl) LONG ACTING CAPSULES

80 mg 120 mg 160 mg

The appearance of these capsules is a registered trademark of Ayerst Laboratories.

Please see brief summary of prescribing information on the next page for further details.

Once-daily For beta-1/beta-2 blockade INDERAL® LA (PROPRANOLOL HCl) LONG ACTING CAPSULES



The appearance of these capsules is a registered trademark of Ayerst Laboratories

BRIEF SUMMARY *(FOR FULL PRESCRIBING INFORMATION SEE PACKAGE CIRCULAR.)*

INDERAL® LA brand of propranolol hydrochloride **(Long Acting Capsules)**

DESCRIPTION. Inderal LA is formulated to provide a sustained release of propranolol hydrochloride. Inderal LA is available as 80 mg, 120 mg, and 160 mg capsules.

CLINICAL PHARMACOLOGY. INDERAL is a nonselective beta-adrenergic receptor blocking agent possessing no other autonomic nervous system activity. It specifically competes with beta-adrenergic receptor stimulating agents for available receptor sites. When access to beta-receptor sites is blocked by INDERAL, the chronotropic, inotropic, and vasodilator responses to beta-adrenergic stimulation are decreased proportionately.

INDERAL LA Capsules (80, 120, and 160 mg) release propranolol HCl at a controlled and predictable rate. Peak blood levels following dosing with INDERAL LA occur at about 6 hours and the apparent plasma half-life is about 10 hours. When measured at steady state over a 24-hour period the areas under the propranolol plasma concentration-time curve (AUCs) for the capsules are approximately 60% to 65% of the AUCs for a comparable divided daily dose of INDERAL tablets. The lower AUCs for the capsules are due to greater hepatic metabolism of propranolol resulting from the slower rate of absorption of propranolol. Over a twenty-four (24) hour period, blood levels are fairly constant for about twelve (12) hours then decline exponentially.

INDERAL LA should not be considered a simple mg for mg substitute for conventional propranolol and the blood levels achieved do not match (are lower than) those of two to four times daily dosing with the same dose. When changing to INDERAL LA from conventional propranolol, a possible need for retitration upwards should be considered especially to maintain effectiveness at the end of the dosing interval. In most clinical settings, however, such as hypertension or angina where there is little correlation between plasma levels and clinical effect, INDERAL LA has been therapeutically equivalent to the same mg dose of conventional INDERAL as assessed by 24-hour effects on blood pressure and on 24-hour exercise responses of heart rate, systolic pressure and rate pressure product. INDERAL LA can provide effective beta blockade for a 24-hour period.

The mechanism of the antihypertensive effect of INDERAL has not been established. Among the factors that may be involved in contributing to the antihypertensive action are (1) decreased cardiac output, (2) inhibition of renin release by the kidneys, and (3) diminution of tonic sympathetic nerve outflow from vasomotor centers in the brain. Although total peripheral resistance may increase initially, it readjusts to or below the pretreatment level with chronic use. Effects on plasma volume appear to be minor and somewhat variable. INDERAL has been shown to cause a small increase in serum potassium concentration when used in the treatment of hypertensive patients.

In angina pectoris, propranolol generally reduces the oxygen requirement of the heart at any given level of effort by blocking the catecholamine-induced increases in the heart rate, systolic blood pressure, and the velocity and extent of myocardial contraction. Propranolol may increase oxygen requirements by increasing left ventricular fiber length, end diastolic pressure and systolic ejection period. The net physiologic effect of beta-adrenergic blockade is usually advantageous and is manifested during exercise by delayed onset of pain and increased work capacity.

In dosages greater than required for beta blockade, INDERAL also exerts a quinidine-like or anesthetic-like membrane action which affects the cardiac action potential. The significance of the membrane action in the treatment of arrhythmias is uncertain.

The mechanism of the antimigraine effect of propranolol has not been established. Beta-adrenergic receptors have been demonstrated in the pial vessels of the brain.

Beta receptor blockade can be useful in conditions in which, because of pathologic or functional changes, sympathetic activity is detrimental to the patient. But there are also situations in which sympathetic stimulation is vital. For example, in patients with severely damaged hearts, adequate ventricular function is maintained by virtue of sympathetic drive which should be preserved. In the presence of AV block, greater than first degree, beta blockade may prevent the necessary facilitating effect of sympathetic activity on conduction. Beta blockade results in bronchial constriction by interfering with adrenergic bronchodilator activity which should be preserved in patients subject to bronchospasm.

Propranolol is not significantly dialyzable.

INDICATIONS AND USAGE. Hypertension: INDERAL LA is indicated in the management of hypertension, it may be used alone or used in combination with other antihypertensive agents, particularly a thiazide diuretic. INDERAL LA is not indicated in the management of hypertensive emergencies.

Angina Pectoris Due to Coronary Atherosclerosis: INDERAL LA is indicated for the long-term management of patients with angina pectoris.

Migraine: INDERAL LA is indicated for the prophylaxis of common migraine headache. The efficacy of propranolol in the treatment of a migraine attack that has started has not been established and propranolol is not indicated for such use.

Hypertrophic Subaortic Stenosis: INDERAL LA is useful in the management of hypertrophic subaortic stenosis, especially for treatment of exertional or other stress-induced angina, palpitations, and syncope. INDERAL LA also improves exercise performance. The effectiveness of propranolol hydrochloride in this disease appears to be due to a reduction of the elevated outflow pressure gradient which is exacerbated by beta-receptor stimulation. Clinical improvement may be temporary.

CONTRAINDICATIONS. INDERAL is contraindicated in 1) cardiogenic shock, 2) sinus bradycardia and greater than first degree block, 3) bronchial asthma, 4) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL.

WARNINGS. CARDIAC FAILURE. Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta blockade may precipitate more severe failure. Although beta blockers should be avoided in overt congestive heart failure, if necessary, they can be used with close follow-up in patients with a history of failure who are well compensated and are receiving digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle.

IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta blockers can, in some cases, lead to cardiac failure. Therefore, at the first sign or symptom of heart failure, the patient should be digitalized and/or treated with diuretics, and the response observed closely; or INDERAL should be discontinued (gradually, if possible).

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following abrupt discontinuance of INDERAL therapy. Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced over at least a few weeks, and the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)—PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

MAJOR SURGERY. The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

INDERAL (propranolol HCl), like other beta blockers, is a competitive inhibitor of be receptor agonists and its effects can be reversed by administration of such agents, e dobutamine or isoproterenol. However, such patients may be subject to protracted sev hypotension. Difficulty in starting and maintaining the heartbeat has also been reported v beta blockers.

DIABETES AND HYPOGLYCEMIA. Beta-adrenergic blockade may prevent the pearance of certain premonitory signs and symptoms (pulse rate and pressure changes acute hypoglycemia in labile insulin-dependent diabetes. In these patients, it may be m difficult to adjust the dosage of insulin.

THYROTOXICOSIS. Beta blockade may mask certain clinical signs of hyperthyroidi Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of sympto of hyperthyroidism, including thyroid storm. Propranolol does not distort thyroid function te

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have b reported in which, after propranolol, the tachycardia was replaced by a severe bradycar requiring a demand pacemaker. In one case this resulted after an initial dose of 5 propranolol.

PRECAUTIONS. *General.* Propranolol should be used with caution in patients with impai hepatic or renal function. INDERAL (propranolol HCl) is not indicated for the treatmen hypertensive emergencies.

Beta adrenoreceptor blockade can cause reduction of intraocular pressure. Patie should be told that INDERAL may interfere with the glaucoma screening test. Withdrawal r lead to a return of increased intraocular pressure.

Clinical Laboratory Tests. Elevated blood urea levels in patients with severe heart disea elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

DRUG INTERACTIONS. Patients receiving catecholamine-depleting drugs such as re pine should be closely observed if INDERAL is administered. The added catecholam blocking action may produce an excessive reduction of resting sympathetic nervous acti which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthost hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility. Long-term studies in animals h been conducted to evaluate toxic effects and carcinogenic potential. In 18-month studie both rats and mice, employing doses up to 150 mg/kg/day, there was no evidence of signific drug-induced toxicity. There were no drug-related tumorigenic effects at any of the dos levels. Reproductive studies in animals did not show any impairment of fertility that attributable to the drug.

Pregnancy. Pregnancy Category C. INDERAL has been shown to be embryotoxi animal studies at doses about 10 times greater than the maximum recommended human dc

There are no adequate and well-controlled studies in pregnant women. INDERAL sho be used during pregnancy only if the potential benefit justifies the potential risk to the fe

Nursing Mothers. INDERAL is excreted in human milk. Caution should be exercised w INDERAL is administered to a nursing woman.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS. Most adverse effects have been mild and transient and h rarely required the withdrawal of therapy.

Cardiovascular. bradycardia, congestive heart failure, intensification of AV block, hy tension, paresthesia of hands, thrombocytopenic purpura, arterial insufficiency, usually of Raynaud type.

Central Nervous System. lightheadedness, mental depression manifested by insom lassitude, weakness, fatigue, reversible mental depression progressing to catatonia, vi disturbances, hallucinations, an acute reversible syndrome characterized by disorientatio time and place, short-term memory loss, emotional lability, slightly clouded sensorium, decreased performance on neuropsychometrics.

Gastrointestinal. nausea, vomiting, epigastric distress, abdominal cramping, diarrh constipation, mesenteric arterial thrombosis, ischemic colitis.

Allergic. pharyngitis and agranulocytosis, erythematous rash, fever combined with act and sore throat, laryngospasm and respiratory distress.

Respiratory. bronchospasm.

Hematologic. agranulocytosis, nonthrombocytopenic purpura, thrombocytope purpura.

Auto-Immune. In extremely rare instances, systemic lupus erythematosus has b reported.

Miscellaneous. alopecia, LE-like reactions, psoriasiform rashes, dry eyes, male im tence, and Peyronie's disease have been reported rarely. Oculomucocutaneous react involving the skin, serous membranes and conjunctivae reported for a beta blocker (practo have not been associated with propranolol.

DOSAGE AND ADMINISTRATION. INDERAL LA provides propranolol hydrochloride sustained-release capsule for administration once daily. If patients are switched from INDE tablets to INDERAL LA capsules, care should be taken to assure that the desired therape effect is maintained. INDERAL LA should not be considered a simple mg for mg substitute INDERAL. INDERAL LA has different kinetics and produces lower blood levels. Retitration be necessary especially to maintain effectiveness at the end of the 24-hour dosing inte

HYPERTENSION—*Dosage must be individualized.* The usual initial dosage is 80 INDERAL LA once daily, whether used alone or added to a diuretic. The dosage may increased to 120 mg once daily or higher until adequate blood pressure control is achie The usual maintenance dosage is 120 to 160 mg once daily. In some instances a dosage of mg may be required. The time needed for full hypertensive response to a given dosag variable and may range from a few days to several weeks.

ANGINA PECTORIS—*Dosage must be individualized.* Starting with 80 mg INDERAL once daily, dosage should be gradually increased at three to seven day intervals until optim response is obtained. Although individual patients may respond at any dosage level, average optimum dosage appears to be 160 mg once daily. In angina pectoris, the value safety of dosage exceeding 320 mg per day have not been established.

If treatment is to be discontinued, reduce dosage gradually over a period of a few we (see WARNINGS).

MIGRAINE—*Dosage must be individualized.* The initial oral dose is 80 mg INDERAL once daily. The usual effective dose range is 160-240 mg once daily. The dosage may increased gradually to achieve optimum migraine prophylaxis. If a satisfactory response is obtained within four to six weeks after reaching the maximum dose, INDERAL LA then should be discontinued. It may be advisable to withdraw the drug gradually over a perio several weeks.

HYPERTROPHIC SUBAORTIC STENOSIS—80-160 mg INDERAL LA once daily.

PEDIATRIC DOSAGE—At this time the data on the use of the drug in this age group are limited to permit adequate directions for use.

REFERENCES

1. Epstein FH, Rosa RM. Adrenergic control of serum potassium. *N Engl J Med* 19 309:1450-1451. **2.** Holland OB, Nixon JV, Kuhnert L. Diuretic-induced ventricular ecto activity. *Am J Med* 1981;70:762-768. **3.** Holme I, Helgeland A, Hjermann I, et al. Treatmer mild hypertension with diuretics. The importance of ECG abnormalities in the Oslo study an MRFIT. *JAMA* 1984;251:1298-1299.

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★ **Official Journal of the California Medical Association, the Idaho Medical Association, the Nevada State Medical Association, the New Mexico Medical Society, the Utah State Medical Association, the Washington State Medical Association and the Wyoming Medical Society.**

★ **Affiliated Clinical Investigation Societies: the Western Association of Physicians; the Western Society for Clinical Investigation; the Western Section, American Federation for Clinical Research; the Western Society for Pediatric Research; the Western Region, Society for Investigative Dermatology.**

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Arthritis pain after 50

Age is no barrier to the benefits of Motrin 600 mg tablets

The pain-relieving power of *Motrin* 600 mg tablets is welcome at any age. The advantages of *Motrin* become more important as patients grow older.

Advanced age has little or no influence on the pharmacokinetics of *Motrin*.

Motrin is as effective as indomethacin in relieving arthritis pain and inflammation. *Motrin* causes significantly fewer CNS effects and about half as many GI complaints as indomethacin.

Motrin relieves pain as effectively as a combination of aspirin 650 mg plus codeine 60 mg, as documented in analgesia studies.

Motrin has no significant effect on clotting factors in patients on coumarin-type anticoagulants in controlled studies. *Motrin* should be used with caution in persons with intrinsic coagulation defects and in those on anticoagulant therapy.

Motrin is rapidly metabolized and does not accumulate. *Motrin* provides better control of therapy, rapid response to dosage adjustment, and permits tailoring dosage to each patient's needs.

New: The Motrin Patient Brochure
An easy-to-read booklet, provided to physicians, that helps patients understand their arthritis therapy... encourages their cooperation.

Helping you to help your patients—
Ask your Upjohn Representative for a complimentary supply.

The confidence that comes from experience...good reason to prescribe

Motrin® 600 mg TABLETS (ibuprofen)

One tablet t.i.d.

Please turn page for a brief summary of prescribing information.

Upjohn The Upjohn Company
Kalamazoo, Michigan 49001

Motrin® Tablets (ibuprofen)

Contraindications: Anaphylactoid reactions have occurred in individuals hypersensitive to *Motrin* Tablets or with the syndrome of nasal polyps, angioedema and bronchospastic reactivity to aspirin, iodides, or other nonsteroidal anti-inflammatory agents.

Warnings: Peptic ulceration and GI bleeding, sometimes severe, have been reported. Ulceration, perforation and bleeding may end fatally. An association has not been established. Use *Motrin* Tablets under close supervision in patients with a history of upper gastrointestinal tract disease, after consulting ADVERSE REACTIONS. In patients with active peptic ulcer and active rheumatoid arthritis, try nonulcerogenic drugs, such as gold. If *Motrin* Tablets are used, observe the patient closely for signs of ulcer perforation or GI bleeding.

Chronic studies in rats and monkeys have shown mild renal toxicity with papillary edema and necrosis. Renal papillary necrosis has rarely been shown in humans treated with *Motrin* Tablets.

Precautions: Blurred and/or diminished vision. scotomata, and/or changes in color vision have been reported. If these develop, discontinue *Motrin* Tablets and the patient should have an ophthalmologic examination, including central visual fields and color vision testing.

Fluid retention and edema have been associated with *Motrin* Tablets; use with caution in patients with a history of cardiac decompensation or hypertension. In patients with renal impairment, reduced dosage may be necessary. Prospective studies of *Motrin* Tablets safety in patients with chronic renal failure have not been done.

Motrin Tablets can inhibit **platelet aggregation** and prolong bleeding time. Use with caution in persons with intrinsic coagulation defects and on anticoagulant therapy.

Patients should report signs or symptoms of **gastrointestinal ulceration** or bleeding, skin rash, weight gain, or edema.

Patients on prolonged **corticosteroid therapy** should have therapy tapered slowly when *Motrin* Tablets are added.

The antipyretic, anti-inflammatory activity of *Motrin* Tablets may mask inflammation and fever.

As with other nonsteroidal anti-inflammatory drugs, borderline elevations of liver tests may occur in up to 15% of patients. These abnormalities may progress, may remain essentially unchanged, or may be transient with continued therapy. Meaningful elevations of SGPT or SGOT (AST) occurred in controlled clinical trials in less than 1% of patients. Severe hepatic reactions, including jaundice and cases of fatal hepatitis, have been reported with ibuprofen as with other nonsteroidal anti-inflammatory drugs. If liver disease develops or if systemic manifestations occur (e.g. eosinophilia, rash, etc.), *Motrin* should be discontinued.

Drug interactions. *Aspirin:* used concomitantly may decrease *Motrin* blood levels.

Coumarin: bleeding has been reported in patients taking *Motrin* and coumarin.

Pregnancy and nursing mothers: *Motrin* should not be taken during pregnancy or by nursing mothers.

Adverse Reactions: The most frequent type of adverse reaction occurring with *Motrin* is gastrointestinal of which one or more occurred in 4% to 16% of the patients.

Incidence Greater than 1% (but less than 3%)–Probable Causal Relationship

Gastrointestinal: Nausea,* epigastric pain,* heartburn,* diarrhea, abdominal distress, nausea and vomiting, indigestion, constipation, abdominal cramps or pain, fullness of GI tract (bloating and flatulence); **Central Nervous System:** Dizziness,* headache, nervousness; **Dermatologic:** Rash* (including maculopapular type), pruritus; **Special Senses:** Tinnitus; **Metabolic/Endocrine:** Decreased appetite; **Cardiovascular:** Edema, fluid retention (generally responds promptly to drug discontinuation; see PRECAUTIONS).

Incidence less than 1%–Probable Causal Relationship**

Gastrointestinal: Gastric or duodenal ulcer with bleeding and/or perforation, gastrointestinal hemorrhage, melena, gastritis, hepatitis, jaundice, abnormal liver function tests; **Central Nervous System:** Depression, insomnia, confusion, emotional lability, somnolence, aseptic meningitis with fever and coma; **Dermatologic:** Vesiculobullous eruptions, urticaria, erythema multiforme, Stevens-Johnson syndrome, alopecia; **Special Senses:** Hearing loss, amblyopia (blurred and/or diminished vision, scotomata, and/or changes in color vision) (see PRECAUTIONS); **Hematologic:** Neutropenia, agranulocytosis, aplastic anemia, hemolytic anemia (sometimes Coombs positive), thrombocytopenia with or without purpura, eosinophilia, decreases in hemoglobin and hematocrit; **Cardiovascular:** Congestive heart failure in patients with marginal cardiac function, elevated blood pressure, palpitations; **Allergic:** Syndrome of abdominal pain, fever, chills, nausea and vomiting; anaphylaxis; bronchospasm (see CONTRAINDICATIONS); **Renal:** Acute renal failure in patients with pre-existing significantly impaired renal function, decreased creatinine clearance, polyuria, azotemia, cystitis, hematuria; **Miscellaneous:** Dry eyes and mouth, gingival ulcer, rhinitis.

Incidence less than 1%–Causal Relationship Unknown**

Gastrointestinal: Pancreatitis; **Central Nervous System:** Paresthesias, hallucinations, dream abnormalities, pseudotumor cerebri; **Dermatologic:** Toxic epidermal necrolysis, photoallergic skin reactions; **Special Senses:** Conjunctivitis, diplopia, optic neuritis; **Hematologic:** Bleeding episodes (e.g., epistaxis, menorrhagia); **Metabolic/Endocrine:** Gynecomastia, hypoglycemic reaction; **Cardiovascular:** Arrhythmias (sinus tachycardia, sinus bradycardia); **Allergic:** Serum sickness, lupus erythematosus syndrome, Henoch-Schönlein vasculitis; **Renal:** Renal papillary necrosis.

*Reactions occurring in 3% to 9% of patients treated with *Motrin*. (Those reactions occurring in less than 3% of the patients are unmarked.)

**Reactions are classified under *"Probable Causal Relationship (PCR)"* if there has been one positive rechallenge or if three or more cases occur which might be causally related. Reactions are classified under *"Causal Relationship Unknown"* if seven or more events have been reported but the criteria for PCR have not been met.

Overdosage: In cases of acute overdosage, the stomach should be emptied. The drug is acidic and excreted in the urine so alkaline diuresis may be beneficial.

Dosage and Administration: Rheumatoid arthritis and osteoarthritis. Suggested dosage is 300, 400, or 600 mg t.i.d. or q.i.d. Do not exceed 2400 mg per day. Mild to moderate pain: 400 mg every 4 to 6 hours as necessary.

Caution: Federal law prohibits dispensing without prescription.

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MED B-7-S

J-3253 June 1983

Upjohn

CONTINUING MEDICAL EDUCATION

(Continued from Page 180)

March 7-9—**Pediatric Review of the Ears, Eyes, Nose and Throat.** Children's Hospital Medical Center of Northern California at High Sierra Hotel, South Lake Tahoe. Thursday-Saturday. Contact: Gretchen Hayes-Dodd, Children's Hospital and Medical Center, 51st and Grove St, Oakland 94609. (415) 428-3334.

March 14-15—**Combined Southern California Pediatric Postgraduate Meeting.** American Association of Pediatricians at Palm Springs. Thursday-Friday. Contact: AAP at (213) 757-1198.

April 10—**Pediatrics: Infections in Infants and Children.** LLU. Wednesday. 4 hrs.

April 17-19—**10th Annual Symposium "Care of the Sick Newborn."** UCI at Hyatt Regency Hotel, Long Beach. Wednesday-Friday. 17 hrs.

April 19-20—**Annual Pediatric Program.** UCD at Sacramento Inn, Sacramento. Friday-Sunday.

May 13-17—**The 15th Annual Review of Pediatrics.** USC at Los Angeles. Monday-Friday. 26 hrs. Fee: $360.

May 15—**Los Angeles Pediatric Society—Annual Spring Meeting** at Los Angeles. Wednesday. Contact: Eve Black, Exec. Sec., PO Box 2022, Inglewood 90305. (213) 757-1198.

May 30-June 1—**Pediatric Rehabilitation Program.** UCD at Doubletree Inn, Monterey. Thursday-Saturday.

PSYCHIATRY

March 29-31—**General Psychiatry Board Review.** UCSF at Golden Gateway Holiday Inn, San Francisco. Friday-Sunday.

April 27-28—**The Cutting Edge 1985—Clinical Applications of Kohut's Theories on Narcissism.** UCSD. Saturday-Sunday. 12.5 hrs.

RADIOLOGY

February 27-March 1—**5th Annual Approaches: Radiologic, Oncology, Biology and Physics.** UCSF at Fairmont Hotel, San Francisco. Wednesday-Friday. Contact: UCSF.

March 6-9—**6th Annual Sierra Radiology Conference.** Sacramento Radiology Society at Hyatt Lake Tahoe, Incline Village. Wednesday-Saturday. 20 hrs. Contact: John P. Walter, MD, Program Director, Sacramento Radiology Research and Education Found., PO Box 19184, Sacramento 95819.

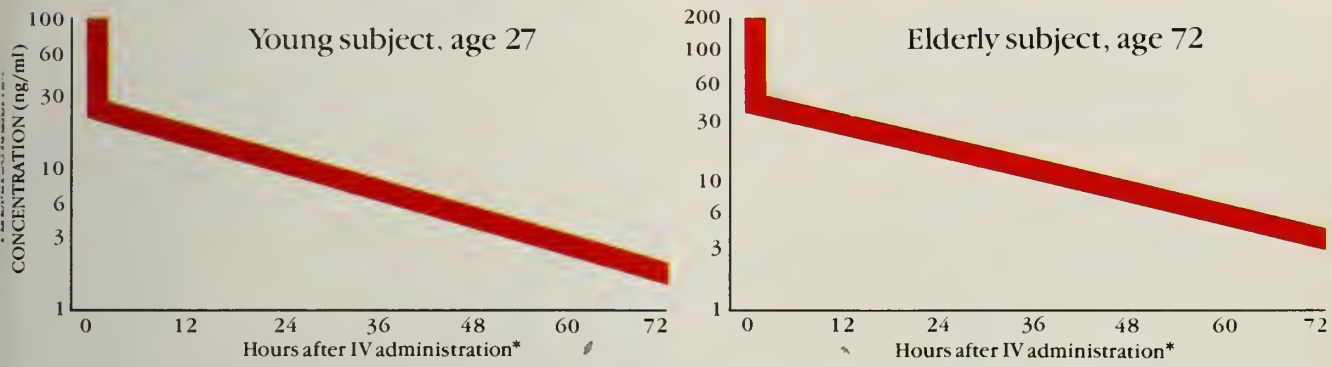
March 11-15—**28th Annual Postgraduate Course in Diagnostic Radiology.** UCSF at Fairmont Hotel, San Francisco. Monday. 33 hrs.

March 18-23—**Diagnostic Imaging 1985.** UCSF at Waiohai Hotel, Kauai. Monday-Saturday. 26 hrs. Fee: $425.

(Continued on Page 194)

Among leading benzodiazepines, only Ativan has proof... pharmacokinetics not significantly altered by age.[1]

Representative charts of comparison testing



Lorazepam is nearly 100 percent bioavailable by the intramuscular and oral routes, as compared to the intravenous. Therefore, data for clearance of intravenous lorazepam are equally applicable to oral lorazepam.

- **Clearance not significantly delayed by age, liver or kidney dysfunction**
- **Cumulative sedative effects seldom a problem**
- **Available in 0.5-mg tablets to facilitate the recommended geriatric starting dosage**

1. Greenblatt DJ: Clinical study, pharmacokinetics and bioavailability in the elderly, Ativan® (lorazepam). Data on file, Wyeth Laboratories.

*Fourteen subjects, aged 60 to 84 years, participated in the study. Twelve subjects, aged 19 to 32 years, served as "young controls." Subject dosage was adjusted for body weight and ranged from 1.5 mg to 3.0 mg of lorazepam. Within the study, lorazepam clearance was monitored following IV, IM and oral administration in the elderly group and following IV administration in the control group. The effect of aging on total clearance of lorazepam was relatively small and not statistically significant. Half-life values following the three different routes of administration were essentially identical.

Only Ativan® (lorazepam)IV

Wyeth Laboratories
Philadelphia, PA 19101

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See important information on following page.

DISTINCTIVE DESIGN 0.5, 1.0 and 2.0 mg

Brief Summary of Prescribing Information.

Indications and Usage: Management of anxiety disorders or short-term relief of symptoms of anxiety or anxiety associated with depressive symptoms. Anxiety or tension associated with stress of everyday life usually does not require treatment with an anxiolytic.

Effectiveness in long-term use, i.e., more than 4 months, has not been assessed by systematic clinical studies. Reassess periodically usefulness of the drug for the individual patient.

Contraindications: Known sensitivity to benzodiazepines or acute narrow-angle glaucoma.

Warnings: Not recommended in primary depressive disorders or psychoses. As with all CNS-acting drugs, warn patients not to operate machinery or motor vehicles, and of diminished tolerance for alcohol and other CNS depressants.

Physical and Psychological Dependence: Withdrawal symptoms like those noted with barbiturates and alcohol have occurred following abrupt discontinuance of benzodiazepines (including convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Addiction-prone individuals, e.g. drug addicts and alcoholics, should be under careful surveillance when on benzodiazepines because of their predisposition to habituation and dependence. Withdrawal symptoms have also been reported following abrupt discontinuance of benzodiazepines taken continuously at therapeutic levels for several months.

Precautions: In depression accompanying anxiety, consider possibility for suicide.

For elderly or debilitated patients, initial daily dosage should not exceed 2mg to avoid oversedation. Terminate dosage gradually since abrupt withdrawal of any antianxiety agent may result in symptoms like those being treated: anxiety, agitation, irritability, tension, insomnia and occasional convulsions. Observe usual precautions with impaired renal or hepatic function. Where gastrointestinal or cardiovascular disorders coexist with anxiety, note that lorazepam has not been shown of significant benefit in treating gastrointestinal or cardiovascular component. Esophageal dilation occurred in rats treated with lorazepam for more than 1 year at 6mg/kg/day. No effect dose was 1.25mg/kg/day (about 6 times maximum human therapeutic dose of 10mg/day). Effect was reversible only when treatment was withdrawn within 2 months of first observation. Clinical significance is unknown; but use of lorazepam for prolonged periods and in geriatrics requires caution and frequent monitoring for symptoms of upper G.I. disease. Safety and effectiveness in children under 12 years have not been established.

ESSENTIAL LABORATORY TESTS: Some patients have developed leukopenia; some have had elevations of LDH. As with other benzodiazepines, periodic blood counts and liver function tests are recommended during long-term therapy.

CLINICALLY SIGNIFICANT DRUG INTERACTIONS: Benzodiazepines produce CNS depressant effects when administered with such medications as barbiturates or alcohol.

CARCINOGENESIS AND MUTAGENESIS: No evidence of carcinogenic potential emerged in rats during an 18-month study. No studies regarding mutagenesis have been performed.

PREGNANCY: Reproductive studies were performed in mice, rats, and 2 strains of rabbits. Occasional anomalies (reduction of tarsals, tibia, metatarsals, malrotated limbs, gastroschisis, malformed skull and microphthalmia) were seen in drug-treated rabbits without relationship to dosage. Although all these anomalies were not present in the concurrent control group, they have been reported to occur randomly in historical controls. At 40mg/kg and higher, there was evidence of fetal resorption and increased fetal loss in rabbits which was not seen at lower doses. Clinical significance of these findings is not known. However, increased risk of congenital malformations associated with use of minor tranquilizers (chlordiazepoxide, diazepam and meprobamate) during first trimester of pregnancy has been suggested in several studies. Because use of these drugs is rarely a matter of urgency, use of lorazepam during this period should almost always be avoided. Possibility that a woman of child-bearing potential may be pregnant at institution of therapy should be considered. Advise patients if they become pregnant to communicate with their physician about desirability of discontinuing the drug. In humans, blood levels from umbilical cord blood indicate placental transfer of lorazepam and its glucuronide.

NURSING MOTHERS: It is not known if oral lorazepam is excreted in human milk like other benzodiazepines. As a general rule, nursing should not be undertaken while on a drug since many drugs are excreted in milk.

Adverse Reactions, if they occur, are usually observed at beginning of therapy and generally disappear on continued medication or on decreasing dose. In a sample of about 3,500 anxious patients, most frequent adverse reaction is sedation (15.9%), followed by dizziness (6.9%), weakness (4.2%) and unsteadiness (3.4%). Less frequent are disorientation, depression, nausea, change in appetite, headache, sleep disturbance, agitation, dermatological symptoms, eye function disturbance, various gastrointestinal symptoms and autonomic manifestations. Incidence of sedation and unsteadiness increased with age. Small decreases in blood pressure have been noted but are not clinically significant, probably being related to relief of anxiety.

Transient amnesia or memory impairment has been reported in association with the use of benzodiazepines.

Overdosage: In management of overdosage with any drug, bear in mind multiple agents may have been taken. Manifestations of overdosage include somnolence, confusion and coma. Induce vomiting and/or undertake gastric lavage followed by general supportive care, monitoring vital signs and close observation. Hypotension, though unlikely, usually may be controlled with Levarterenol Bitartrate Injection U.S.P. Usefulness of dialysis has not been determined.

Ativan® (lorazepam) **for Anxiety**

DOSAGE: Individualize for maximum beneficial effects. Increase dose gradually when needed, giving higher evening dose before increasing daytime doses. Anxiety, usually 2-3mg/day given b.i.d. or t.i.d.; dosage may vary from 1 to 10mg/day in divided doses. For elderly or debilitated, initially 1-2mg/day; insomnia due to anxiety or transient situational stress, 2-4mg h.s.

HOW SUPPLIED: 0.5, 1.0 and 2.0mg tablets.

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CONTINUING MEDICAL EDUCATION

(Continued from Page 192)

April 14-19—**Adult and Pediatric Radiology for Emergency Physicians.** UCSD at Waiohai Hotel, Kauai. Sunday-Friday. 21 hrs. Fee: $315-430.

April 29-May 3—**5th Annual Residents Radiology Review Course.** UCSD at Town and Country Inn, San Diego. Monday-Friday.

SPORTS MEDICINE

March 18-22—**University of Hawaii Sports Medicine Course.** Ohio State University at Princess Kaiulani Hotel, Waikiki, HI. Monday-Friday. 18 hrs. Fee: $280. Contact: Ms. Joy Lewis, Box CEW-CCECS, 2530 Dole St., Honolulu, HI 96822. (808) 948-8244.

SURGERY

February 23—**General Surgery.** UCSF at Fresno. Saturday. 7.5 hrs.

March 4-8—**Surgical Forum.** Society of Graduate Surgeons of Los Angeles County at Ambassador Hotel, Los Angeles. Monday-Friday. 31 hrs. Fee: $400. Contact: Director of Medical Education, Society of Graduate Surgeons, 5820 Wilshire Blvd., #500, Los Angeles 90036.

March 8-10—**Surgery for Sleep Apnea Snoring—Current Advances.** UCI at Marriott Hotel, Newport Beach. Friday-Sunday. 11 hrs.

March 18-22—**Basic Microsurgery Training Workshop.** UCSD. Monday-Friday. 34 hrs. Fee: $1,200. Contact: UCSD.

March 25-29—**Advanced Microsurgery Training Workshop.** UCSD. Monday-Friday. 34 hrs. Fee: $1,200. Contact: UCSD.

April 1-5—**Basic Microsurgery Training Workshop.** UCSD. Monday-Friday. 34 hrs. Fee: $1,200.

April 1-5—**12th Annual Spring Meeting of American College of Surgeons** at Hilton Hawaiian Village Hotel, and Westin Ilikai Hotel, Hawaii. Sunday-Thursday. Contact: ACS, 55 E. Erie St., Chicago, Il 60611.

April 24-26—**Postgraduate Course in General Surgery.** UCSF at Hilton Hotel, San Francisco. Wednesday-Thursday.

May 2-4—**Postgraduate Course in General Surgery.** UCSF at St. Francis Hotel, San Francisco. Thursday-Saturday. 15 hrs.

May 13-17—**Basic Microsurgery Training Workshop.** UCSD. Monday-Friday. 34 hrs. Fee: $1,200.

May 30-31—**14th Annual Neurosurgery and 8th Annual Neurosurgical Nurses Conference.** UCSF at San Francisco Hilton Hotel, San Francisco. Thursday-Friday. 15.5 hrs.

(Continued on Page 276)

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WARNING
This drug is not indicated for initial therapy of edema or hyper tension. Edema or hypertension requires therapy titrated t the individual. If this combination represents the dosage s determined, its use may be more convenient in patier management. Treatment of hypertension and edema is nc static, but must be reevaluated as conditions in each patier warrant.

Contraindications: Concomitant use with other potassiu sparing agents such as spironolactone or amiloride. Further i in anuria, progressive renal or hepatic dysfunction, hyperkalen Pre-existing elevated serum potassium. Hypersensitivity to eit component or other sulfonamide-derived drugs.

Warnings: Do not use potassium supplements, dietary or oth wise, unless hypokalemia develops or dietary intake of pot sium is markedly impaired. If supplementary potassium is need potassium tablets should not be used. Hyperkalemia can oc and has been associated with cardiac irregularities. It is m likely in the severely ill, with urine volume less than liter/day, the elderly and diabetics with suspected or confirm renal insufficiency. Periodically, serum K^+ levels should determined. If hyperkalemia develops, substitute a thiazide alo restrict K^+ intake. **Associated widened QRS complex arrhythmia requires prompt additional therapy.** Thiazides cr the placental barrier and appear in cord blood. Use in pregnai requires weighing anticipated benefits against possible hazar including fetal or neonatal jaundice, thrombocytopenia, ot adverse reactions seen in adults. Thiazides appear and triamtere may appear in breast milk. If their use is essential, the pati should stop nursing. Adequate information on use in childre not available. Sensitivity reactions may occur in patients with without a history of allergy or bronchial asthma. Possible exac bation or activation of systemic lupus erythematosus has b reported with thiazide diuretics.

Precautions: Do periodic serum electrolyte determinations [p ticularly important in patients vomiting excessively or receiv parenteral fluids, and during concurrent use with amphotenci or corticosteroids or corticotropin [ACTH]). Periodic BUN a serum creatinine determinations should be made, especiall the elderly, diabetics or those with suspected or confirmed re insufficiency. Cumulative effects of the drug may develop patients with impaired renal function. Thiazides should be u with caution in patients with impaired hepatic function. They precipitate coma in patients with severe liver disease. Obse regularly for possible blood dyscrasias, liver damage, ot idiosyncratic reactions. Blood dyscrasias have been reporte patients receiving triamterene, and leukopenia, thrombocy penia, agranulocytosis, and aplastic and hemolytic anemia h been reported with thiazides. Thiazides may cause manifestat of latent diabetes mellitus. The effects of oral anticoagulants n be decreased when used concurrently with hydrochlorothiazi dosage adjustments may be necessary. Clinically insignific reductions in arterial responsiveness to norepinephrine h been reported. Thiazides have also been shown to increase paralyzing effect of nondepolarizing muscle relaxants such tubocurarine. Triamterene is a weak folic acid antagonist. periodic blood studies in cirrhotics with splenomegaly. Antihyp tensive effects may be enhanced in post-sympathectomy patie Use cautiously in surgical patients. Triamterene has been fou in renal stones in association with the other usual calculus co ponents. Therefore, 'Dyazide' should be used with caution patients with histories of stone formation. A few occurrences acute renal failure have been reported in patients on 'Dyaz when treated with indomethacin. Therefore, caution is adv in administering nonsteroidal anti-inflammatory agents v 'Dyazide'. The following may occur: transient elevated BUN creatinine or both, hyperglycemia and glycosuria (diabetic insu requirements may be altered), hyperuricemia and gout, digit intoxication (in hypokalemia), decreasing alkali reserve with p sible metabolic acidosis. 'Dyazide' interferes with fluoresc measurement of quinidine. Hypokalemia is uncommon v 'Dyazide', but should it develop, corrective measures should taken such as potassium supplementation or increased diet intake of potassium-rich foods. Corrective measures should instituted cautiously and serum potassium levels determin Discontinue corrective measures and 'Dyazide' should laborat values reveal elevated serum potassium. Chloride deficit n occur as well as dilutional hyponatremia. Concurrent use v chlorpropamide may increase the risk of severe hyponatren Serum PBI levels may decrease without signs of thyroid dist bance. Calcium excretion is decreased by thiazides. 'Dyazi should be withdrawn before conducting tests for parathyr function.

Thiazides may add to or potentiate the action of other antihyp tensive drugs.

Diuretics reduce renal clearance of lithium and increase the of lithium toxicity.

Adverse Reactions: Muscle cramps, weakness, dizziness, he ache, dry mouth; anaphylaxis, rash, urticaria, photosensiti purpura, other dermatological conditions; nausea and vomiti diarrhea, constipation, other gastrointestinal disturbances; p tural hypotension (may be aggravated by alcohol, barbitural or narcotics). Necrotizing vasculitis, paresthesias, icterus, p creatitis, xanthopsia and respiratory distress including pneum nitis and pulmonary edema, transient blurred vision, sialaden and vertigo have occurred with thiazides alone. Triamterene h been found in renal stones in association with other usual calcu components. Rare incidents of acute interstitial nephritis h been reported. Impotence has been reported in a few patients 'Dyazide', although a causal relationship has not been establish

Supplied: 'Dyazide' is supplied as a maroon and white capsu in bottles of 1000 capsules; Single Unit Packages (unit-do of 100 (intended for institutional use only); in Patient-Pa unit-of-use bottles of 100.

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Current Trends in Antifertility Vaccine Research

DANA C. COVEY, MD, *Shreveport, Louisiana, and* KEVIN D. O'BRIEN, MD, *and* DONALD E. MOORE, MD, *Seattle*

We review the major advances that have recently occurred in the area of antifertility vaccines by examining the immunogenic potential of gamete, embryonic and placental antigens. In human trials using β-human chorionic gonadotropin coupled with tetanus toxoid as the immunogen, the major problems with antifertility vaccines relate to specificity and maintaining an adequate antibody titer to disrupt gestation. Possible complications include cross-reaction with other body tissues, immune complex deposition, cytotoxicity, impaired immunologic tumor surveillance and nonreversibility.

(Covey DC, O'Brien KD, Moore DE: Current trends in antifertility vaccine research. West J Med 1985 Feb; 142:197-202)

Although a number of methods are available today for contraception, none of them are absolutely safe, free from discomfort and universally acceptable. Thus, research continues toward developing a more effective means of fertility regulation. Among these new approaches, active immunization against one or more antigens involved in the reproductive process bears particular promise because it would preclude the disadvantages associated with a daily oral drug regimen.

Ideally, an antifertility vaccine should have the following properties: reasonable titers of antibodies to the immunogen should develop in all recipients; the immunity should persist for a reasonable amount of time, say 6 to 18 months, so that numerous booster injections are not required; the antifertility effect should be reversible; noxious adjuvants such as Freund's complete adjuvant should be avoided; antibodies produced should be specific to the reproductive process without cross-reacting with other body components, and there should be no serious side effects (Table 1).

A number of factors governs the specificity of the immune response to a given antigen. These include the type of antigen, method of presentation, the route of administration and the adjuvant used. Several other factors affect the duration of immunity. These include the persistence of the antigen in vivo, clonal expansion, T- and B-cell cooperation and the production of memory lymphocytes.

In this review, we consider immunologic fertility control in terms of three broad classes of antigens: gamete, embryonic and placental. We focus on active rather than passive immunization because the former method is more efficacious and amenable to large-scale use.

Gamete Antigens

Zona Pellucida

The zona pellucida, an acellular gelatinous layer, surrounds the mammalian oocyte and preimplantation embryo. The zona pellucida prevents polyspermia and blocks penetration of sperm by other species.[1,2] This layer breaks away just before implantation either by a hatching mechanism involving embryo pulsation, by uterine proteolytic activity or by a combination of both.[3] The following features make the zona pellucida an attractive target for immunologic contraception: it is a unique structure, immunization could prevent conception and therefore not act as an abortifacient and there may be as many as four antigenic sites on this structure that might promote specificity and simplicity in antibody production.[4]

The zona-specific antigens develop at the stage of the secondary follicle, persist throughout the ovulation stage and are intact when the sperm-ovum interaction occurs.[5] These antigens are also detectable on the zonae of embryos at the morula and blastocyst stages and are retained until zona shedding during implantation.[6] Thus there is ample opportunity for specific circulating antibodies to bind with zona antigens. Antibodies raised against zona

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Drs Covey and O'Brien are recipients of the Robert H. Williams and Robert L. Van Citters Research Awards, respectively, from the University of Washington.

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Submitted, revised, April 2, 1984.

Reprint requests to Kevin D. O'Brien, MD, Department of Medicine, RG-20, University of Washington School of Medicine, Seattle, WA 98195.

ABBREVIATIONS USED IN TEXT

DS_5-hCG-β-hem = a highly specific derivative of β-human chorionic gonadotropin
FSH = follicle-stimulating hormone
hCG = human chorionic gonadotropin
β-hCG-TT = β-hCG coupled with tetanus toxoid
hPL = human placental lactogen
LDH-C_4 = an isoenzyme of lactate dehydrogenase
LH = luteinizing hormone
OLHβ = β-subunit of ovine luteinizing hormone
PP_5 = placental protein-5
SP_1 = Schwangershaft's protein-1

antigens can inhibit fertility, presumably by preventing sperm attachment and passage through the zona.[7] Although zona pellucida antigens are tissue-specific, they are not species-specific; it has been shown that human and porcine zonae (and other species) contain an immunologically similar cross-reacting antigen.[8] Antiserum produced against a purified 60,000 molecular weight component isolated from porcine zonae inhibited in vitro adherence of homologous sperm to antiserum-pretreated human and monkey zonae.[9] Thus the porcine zona pellucida may serve as an antigenic source for the development of a human contraceptive vaccine. Its efficacy would depend on whether sufficiently high antibody titers could be achieved and whether tissue specificity could be assured.

Spermatozoa

In most research in this area two sperm-specific antigens have been used: Lactate dehydrogenase (LDH-C_4) or acrosin. LDH-C_4 (formerly called LDH-X) is an isoenzyme that is specific to the acrosome of spermatozoa. Mouse LDH-C_4 has been isolated in pure form and antibody to it cross-reacts with the human sperm enzyme.[10] Anti-LDH-C_4 causes reduced fertility in rabbits.[11] More promising results were obtained in baboons that were immunized with both human and murine LDH-C_4.[12] Seven of eight matings subsequent to immunization were infertile and the one pregnancy that occurred was in an animal with undetectable antibody titers.

Acrosin is a protease also present in the acrosome. It has been implicated as the enzyme responsible for penetration of the zona pellucida by spermatozoa, and may play a role in the acrosome reaction.[13,14] Studies have shown that acrosin inhibitors can prevent fertilization of the ovum.[15-17] Additional work has shown that immunization of ewes with partially purified ram acrosin reduced but did not eliminate fertility.[18] Because a single ejaculation introduces millions of spermatozoa into the female reproductive tract and only one sperm is required for fertilization, it may be difficult to achieve sufficiently high antibody titers in the oviductal fluid to ensure neutralization of every sperm. Studies in this area to date have shown only reduced fertility or incomplete sterility.

Embryonic Surface Antigens

Several investigators have studied immunization against embryonic cell surface antigens as a means of fertility prevention. An embryonic antigen useful for fertility control should have the following characteristics: the antigen must be present on the embryonic surface in a density and for a length of time that would allow immunologic recognition and destruction of the cell; mediators of immune destruction should have access to the embryo that is unimpeded by physical barriers such as zona pellucida, decidual tissue or reproductive tract epithelium, and the embryonic target antigens should lack determinants found in adult tissues.

Alloantigens

Alloantigens are controlled by histocompatibility genes, and their expression in mouse embryos has been extensively studied.[19,20] In mice, the major histocompatibility (H-2) antigens are found on the embryonic cell surface in the early blastocyst stage, and the minor histocompatibility antigens may be expressed at the first cleavage stages.[21,22] However, murine alloantigens may be available for recognition only during the preimplantation periods, as their expression on the trophectoderm surface is reduced sharply with the initiation of implantation. This short period of expression and the highly polymorphic nature of alloantigens are felt to make them poor candidates for use in immunocontraception.[23]

Oncofetal Antigens

Oncofetal antigens have been detected on various spontaneous, chemically induced and virally transformed tumors. They are also detectable on embryonic cell surfaces.[24,25] F-9 teratocarcinoma oncofetal antigens are the most well studied of this group. In one study[26] female mice immunized with F-9

TABLE 1.—*Comparison of 'Ideal' Properties of Possible Antifertility Antigens*

	'Ideal' Properties					
Antigens	*High Antibody Titers*	*Persistence of Immunity*	*Possible Reversibility*	*Safe, Effective Adjuvant Available*	*Antibody Specificity*	*Free of Complications*
Zona pellucida	±	+	+	−	+	±
Spermatozoa						
LDH-C_4	−	+	±	−	+	±
Acrosin	−	+	±	−	+	±
Embryonic alloantigens	±	±	±	−	−	±
Oncofetal antigens	±	±	±	−	±	±
Structural trophoblastic antigens	±	±	±	−	±	±
Placental enzymes	−	−	−	−	−	−
Schwangershaft's protein-1	±	±	±	−	−	±
Placental protein-5	±	±	±	−	±	±
Human placental lactogen	±	−	±	−	−	−
Human chorionic thyrotropin	±	−	±	−	−	−
Human chorionic gonadotropin	±	±	±	−	+	±

LDH-C_4 = lactate dehydrogenase isoenzyme C_4, ± = equivocal, + = present, − = absent

cells showed a reduction in fertility. However, of three F-9 immunized mice that became pregnant, teratocarcinoma developed in one, and all fetuses of another were severely growth retarded.

Structural Trophoblastic Antigens

Because trophoblast is normally found only in cases of pregnancy, antigenic determinants unique to this tissue would offer potential sites for antibody binding. In mice it has been possible to obtain relatively pure trophoblast (called ectoplacental cone trophoblast) by dissecting the early postimplantation conceptus before infiltration of other tissues. It has thus been possible to raise a heterologous antiserum that shows specific binding to trophoblast cell populations.[23] The antigens differ from alloantigenic determinants in that they are not lost at the time of implantation. The difficulty with this approach for humans is obtaining sufficient quantities of trophoblast-specific antigens to effect immunization. Also, it is not known in humans whether or not antibodies to trophoblastic antigens would cross-react with other tissue antigens.

Placental Antigens

Placental proteins are unique to pregnancy and would provide logical targets for the action of an antifertility vaccine. The ideal antigen would be specific to early gestation, required for maintaining pregnancy and be present in trace amounts to facilitate neutralization by specific antibodies. A number of placental proteins have been characterized, including human placental lactogen (also known as human chorionic somatomammotropin), human chorionic thyrotropin, human chorionic gonadotropin (hCG), β_1-glycoproteins and placental enzymes.[27]

Placental enzymes. These include 17β- and 3β-hydroxysteroid dehydrogenases, cystine aminopeptidase and heat-stable alkaline phosphatase. However, these enzymes are not suitable candidates for an antifertility vaccine as they lack the requisite immunologic specificity.

β_1-Glycoproteins. Two human placental β_1-glycoproteins have been purified, Schwangershaft's protein-1 (SP_1) and placental protein-5 (PP_5), having molecular weights of 90,000 and 50,000, respectively.[27] Passive immunization of fertile female monkeys with anti-human SP_1 resulted in decreased fertility, although isoimmunization yielded less promising results.[28] Problems with using SP_1 as a basis for fertility control include the large amounts that are present in the placenta and its lack of tissue specificity.[29] On the other hand, PP_5 has been found to be a more potent antifertility agent than SP_1 and is capable of causing a significant reduction in fertility in monkeys immunized with this antigen.[27] However, the physiologic role of this glycoprotein during pregnancy has not been elucidated.

Human placental lactogen and human chorionic thyrotropin. Human placental lactogen (hPL) is secreted by the trophoblast and is detectable in serum at about the sixth gestational week. Although anti-hPL in serum was able to disrupt pregnancy in rats, mice and baboons, active immunization of baboons against baboon placental lactogen did not result in abortions.[27] Due to hPL's immunologic similarity to pituitary growth hormone, it would have to be suitably modified to avoid cross-reactivity. Human chorionic thyrotropin, like hPL, has considerable immunologic cross-reactivity with its pituitary counterpart and major molecular modifications would have to be made to obviate this problem.

Human Chorionic Gonadotropin

Human chorionic gonadotropin has received much attention as a target for an antifertility vaccine due to its unique physiologic role in human reproduction. This hormone is normally produced only during pregnancy and is not present in nonpregnant women. After implantation, hCG is secreted by the trophoblast into the maternal circulation, rescues the corpus luteum from degeneration and stimulates it to secrete estrogen and progesterone.[30,31] Not until placental steroid production surpasses that of the corpus luteum at the ninth gestational week does the corpus luteum become unnecessary for endometrial support. hCG thus bridges the transition from ovarian to placental steroid function. Because hCG travels via the maternal circulation from the trophoblast to the corpus luteum, it is subject to inactivation by specific circulatory antibodies. It has been postulated that serum antibodies with a binding capacity of 20 ng of hCG per ml of serum would be sufficient to interrupt pregnancy.[32]

Whether hCG is secreted by the blastocyst before or after implantation has yet to be resolved. Using a radioreceptor assay that detects both hCG and human luteinizing hormone (LH), Saxena and co-workers found increased levels of hCG as early as six days after ovulation.[33] Other investigators, however, did not detect a significant rise in plasma hCG until 9 to 13 days following ovulation, precluding the likelihood that hCG is secreted before implantation of the blastocyst.[34] Regardless of the chronology of hCG secretion, it is of paramount importance during the first trimester of pregnancy.

Human chorionic gonadotropin, a glycoprotein of molecular weight 39,000, is composed of an α- and a β-subunit.[35] The β-subunit, with a molecular weight of 23,000,[36] is responsible for the hormonal identity of hCG.[37] The structure of hCG is similar to that of the pituitary glycoproteins, thyroid-stimulating hormone (thyrotropin), follicle-stimulating hormone (FSH) and luteinizing hormone. As in the case of hCG,the β-subunit of these pituitary hormones confers to each its own biologic specificity. The α-subunits of hCG, LH, FSH and thyrotropin are nearly identical.[37] However, β-hCG has an additional 30 amino acid residues at its carboxyterminus that are not found in the β-subunits of the other glycoprotein hormones, with four of the additional serine residues possessing carbohydrate side chains.[38] Due to the similar amino acid sequences of hCG and human LH, use of the former as an antigen would necessitate that it be highly purified; otherwise a high cross-reactivity with human LH would exist.

The considerable amino acid homology between the β-subunits of hCG and human LH and the low molecular weight of β-hCG promoted studies to increase its specific antigenic qualities. These included (1) coupling the subunit to a protein carrier[39]; (2) using enzyme-cleaved fragments from the unique COOH-terminus of the β-subunit[40]; (3) constructing synthetic peptides with amino acid structures similar to the COOH-terminal region[41]; (4) using synthetic COOH-terminal peptide conjugated to antigenic carrier proteins,[42] and (5) chemical modification of the β-subunit with specific functional reagents.[27] The rationale for these approaches was supported by reports that indicate that antibodies against β-hCG could discriminate hCG from human LH.[43,44]

Spatial configuration of the molecule also plays an important role in the antigenicity of β-hCG. Partial reduction and s-carboxamidomethylation of the β-subunit induces a change in its three-dimensional structure that leads to preferential loss of human LH and retention of hCG immunoactivity.[45] Lerario and associates found that hCG-specific determinants, which reside in the variable region of the β-subunit, are predominantly conformational rather than sequential in nature.[46] They also found that antigenic determinants, usually buried when β-hCG is combined with its complementary α-subunit, are subsequently uncovered when β-hCG dissociates. Antibodies produced against the dissociated β-subunit were not as sensitive as antisera to the endogenous intact hormone, or the β-hCG coupled to a nonhuman α-subunit.

Stevens and colleagues used β-hCG hapten coupled with *p*-aminobenzene-sulfonic acid to immunize baboons.[27] The antibodies produced showed cross-reactivity with human but only weakly with baboon LH. Talwar and co-workers showed that injection of β-hCG coupled with tetanus toxoid (β-hCG-TT) elicited a desirable antibody response to the native hormone in animals.[47] They reported that anti-β-hCG-TT sera raised in various species neutralized the biologic activity of hCG in three of four test systems. Additional work showed that preimmunization with tetanus toxoid carrier would enhance neutralizing antibody production to β-hCG.[48] Studies in rhesus monkeys showed that hCG administered after immunization with β-hCG-TT resulted in a decline in circulating antibody titers. Therefore, these antibodies were able to recognize and bind the hCG molecule.[49] When human LH was administered in lieu of hCG, there was no detectable decline in anti-hCG titer. Native hCG did not act as a booster to induce an anamnestic response.[5]

Bahl and co-workers have developed a highly specific derivative of β-hCG (DS_5-hCG-β-hem) by the controlled reduction and alkylation of disulfide bonds followed by conjugation to keyhole limpet hemocyanin. Rabbit antibody to DS_5-hCG-β-hem specifically bound hCG with no significant cross-reactivity with human LH and other polypeptide hormones.[27] The antibody neutralized in vivo the effect of hCG on ovarian ascorbic acid content without affecting human LH activity. It also inhibited hCG-induced rat uterine weight gain.

To date, only β-hCG-TT has been tested in phase I clinical trials; 15 young adult women who had previously undergone tubal ligation were immunized with this conjugate.[32] Antibodies developed in 14 of the women, and no adverse effects were noted. Unfortunately, sufficiently high anti-hCG titers to ensure adequate binding of maternal hCG did not develop. Interestingly, high antibody titers against the tetanus toxoid carrier protein were produced. This discrepancy in antibody response to the two components of the conjugate could be explained by the following: β-human chorionic gonadotropin is an isoantigen and therefore not a potent immunogen in its own right; because the tetanus toxoid carrier contains polymers with molecular weights 100 times greater than that of β-hCG, its large size may impede recognition of the hapten, resulting in decreased antibody production; and the use of a bifunctional reagent might join not only hapten to carrier, but also β-hCG to β-hCG and carrier to carrier, thus reducing the net dose of immunogenic polymer.

Additional human trials have been conducted to further evaluate β-hCG-TT. Recently 23 women were immunized with this conjugate, but peak titers could not be sustained and most showed a variable pattern of antibody response.[50]

Although not of placental origin, the β-subunit of the ovine pituitary glycoprotein, luteinizing hormone (OLHβ), is able to elicit production of antibodies in the serum of rhesus monkeys that cross-react strongly with rhesus chorionic gonadotropin with resultant reduced fertility.[51] The antifertility effect of anti-OLHβ is probably due to prevention of corpus luteum rescue.[52] Anti-OLHβ was also able to bind hCG,[51] which leads to the possible extrapolation of this technique to humans.

Adjuvants

The problem of sufficient antibody production to any reproductive tract immunogen probably also extends to the type of adjuvant used. Although the use of alum-precipitated antigen has proved to be a safe vehicle for human vaccination, it stimulates insufficient antibody response to β-hCG or other isoantigens. Talwar points out that unless Freund's complete adjuvant is used, investigators have been unsuccessful in stimulating antibodies to synthetic fragments of β-hCG.[53] Freund's complete adjuvant, although a potent adjuvant, causes extensive and disfiguring granuloma formation and therefore is not acceptable for human use.

To achieve a state of enhanced immune responsiveness to a putative reproductive tract antigen, an adjuvant may act in one or more of three ways.[54] First, a slow release of antigen from the site of deposition may prolong and thereby potentiate the antigenic stimulus. Second, the adjuvant could stimulate the mononuclear phagocyte system, causing rapid ingestion or more effective processing of antigen and enhanced lymphocytic response. Third, adjuvants might evoke a generalized immune response, such as a direct action on lymphocytes or an acceleration of cellular differentiation.

A number of adjuvants have been tested for possible use with an antifertility vaccine. Muramyl dipeptide or one of its analogs has recently been shown to be a highly effective adjuvant. It has the following advantages: it is a simple synthetic compound with many analogs, it is soluble in water, it is not cytotoxic and it is not antigenic in its own right.[55] The use of muramyl dipeptide with β-hCG-TT is in the initial stages of investigation.[56] Also, Covey and associates have shown that *Corynebacterium parvum* may potentiate neutralizing antibody production to β-hCG-TT.[57] Other adjuvants considered include thymic factor, lavamisole, tilorone, liposomes and *Bordetella pertussis*. Perhaps one of the foregoing adjuvants or a new immunoenhancing compound such as lynestrenol[58] will provide the breakthrough needed to produce a safe, effective vaccine.

Potential Complications of Antifertility Vaccines

Complications Associated With Active Immunization

Immunization may result in anaphylactic reactions mediated by mast-cell-bound IgE antibodies. Factors that predispose a person to such reactions include a small antigenic dose[59]; genetic susceptibility[60]; the use of certain adjuvants, especially pertussis,[61,62] and IgA deficiency.[63] Determining the presence of antigen-specific serum IgE is possible by the radioallergosorbent test and may be helpful in averting this potentially life-threatening problem. Other complications of

active immunizations include delayed hypersensitivity and Arthus reactions.

Possible Complications Associated With hCG or hCG-Subunit Immunizations

Because the α-subunit of hCG is nearly identical to the α-subunits of thyrotropin, FSH and LH, immunization with the intact hCG molecule could cause production of antibodies that cross-react with these other hormones.[36] These cross-reactive antibodies could then neutralize LH, FSH and thyrotropin and cause decreased function of the hormones' target organs. Immunization with the β-subunit of hCG would avoid the production of antibodies that cross-react with thyrotropin and FSH. However, the β-subunits of LH and hCG are very similar in structure and the potential for formation of antibody that reacts with LH would still exist with β-hCG immunization.

Immunization with pituitary hormones or pituitary hormone analogs may damage the pituitary gland itself. There is indirect evidence that antibodies to pituitary hormones may damage the pituitary gland, either via direct cytotoxicity[64,65] or by forming insoluble complexes on the cell surface and eliciting an Arthus reaction.[66]

Serum sickness is another potential complication of hCG immunization because cross-reactive antibodies could also form circulating immune complexes with pituitary hormones. However, because circulating immune complexes most readily form in situations of slight antigen excess,[67] the extremely low circulating levels of thyrotropin, FSH and LH make this complication unlikely.

Finally, because human malignant tumors may express hCG or embryonic antigens on their surfaces, it has been postulated[68] that masking of these surface antigens by non-complement-fixing antibodies could impede T-lymphocyte recognition and destruction—that is, immunologic surveillance. Also, Hurtenbach and Shearer[69] have shown that immunizing mice with sperm antigens impairs cancer immunosurveillance through generation of T-suppressor lymphocytes.

Possible Complications Associated With Sperm Antigen Immunizations

In 1966 Paterson[70] reported that in Lewis rats immunized with testicular antigens, pathologic changes developed in their brains that were histologically consistent with the findings in cases of allergic encephalomyelitis. However, the possibility that the rats were infected with viral encephalomyelitis, a common disease in Lewis rats, was not excluded.[68]

Other studies have shown the existence of cross-reactive antigens found in both mouse sperm and fetal tissue.[68,71] This raises the possibility that antisperm antibodies could cross-react with fetal tissue and harm or modify fetal development. Cross-reactive antisperm antibodies might also interfere with immunologic surveillance of fetal-antigen-secreting tumors.

Finally, Tung[68] has reported that amyloidosis has developed in sperm-immunized guinea pigs. Therefore, he has raised the question of whether widespread amyloidosis could occur in humans immunized with sperm antigens.

Conclusion

For an antifertility vaccine to be efficacious, it must cause an adequate antibody titer even in poor responders. In this regard, adjuvant research looks to improve these titers. Both natural and synthetic adjuvants are being tested. It is estimated that another 10 to 15 years of sustained, high-priority effort will be needed to produce a workable vaccine using either β-hCG or one of the other compounds.[72] An effective antifertility vaccine should become a reality when the right match of antigen and adjuvant is discovered.

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Amebiasis Presenting as Pleuropulmonary Disease

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Seven patients with amebic liver abscess presenting as pleuropulmonary disease were admitted to hospital initially because of pulmonary symptoms and were found to have amebic liver disease. Three categories of pleuropulmonary involvement included reactive inflammation of the pleura or lung, rupture of a hepatic abscess into the pleural space and rupture of a hepatic abscess into the bronchial airways. The preferred medical treatment is with metronidazole, but rupture of a hepatic amebic abscess into the pleural space requires drainage in addition to medical therapy. In contrast, rupture into the bronchus may provide spontaneous drainage so that only medical therapy is needed. Recovery from amebiasis in all three categories is generally complete. Morbidity and mortality increase with failure to correctly identify amebic infection of the liver as the underlying cause. Because, in new cases, no findings specifically suggest that pleuropulmonary disease is a complication of hepatic amebic abscess, this possibility needs to be considered, especially in persons who are at risk of having been infected with amebae.

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Extraintestinal amebiasis occasionally presents as pleuropulmonary disease with few clues to suggest the presence of an underlying hepatic abscess[1]; in such cases, the correct diagnosis may be reached only with great difficulty and after considerable delay.[1-3] We report the cases of seven patients whose presenting symptoms led to a primary consideration of intrathoracic disease, but who, in fact, had pleuropulmonary complications of amebic liver abscess. These complications fell into one of three pathophysiologic categories: (1) reactive inflammatory response of the pleura or lung resulting in pleural effusion or pneumonitis—in this situation, the hepatic abscess being confined to the liver; (2) rupture of the abscess into the pleural space resulting in empyema, and (3) erosion directly into the bronchial airways, resulting in consolidation, lung abscess or hepatobronchial fistula, with or without a pleural effusion or empyema. This study emphasizes the need to consider amebic infections in the evaluation of thoracic complaints, especially in recent Latin-American immigrants and travelers returning from endemic areas.

Patients

The seven patients described here were referred for pulmonary consultation at one of the Baylor College of Medicine-affiliated hospitals during the 18-month period from December 1980 to May 1982. The clinical course, laboratory data, roentgenographic data and treatment of each are summarized in Table 1.

The mean age of the five men and two women was 39 years (range, 21 to 70). Six of the seven were Mexican immigrants who had resided in the United States for an average of 15.6 months (range, 5 to 36) before admission. The seventh patient had traveled to Mexico three months before he became ill.

Pulmonary symptoms, generally subacute in nature, represented the chief complaint in all patients. These included chest pain (three patients), dyspnea (one), persistent cough (one), hemoptysis (one) and thick, "chocolate" sputum (one). After the diagnosis of amebiasis had been established, a vague history of abdominal symptoms such as abdominal

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ABBREVIATIONS USED IN TEXT

CIE = counterimmunoelectrophoresis
CT = computed tomography
LDH = lactic dehydrogenase
P_{CO_2} = partial carbon dioxide pressure
P_{O_2} = partial oxygen pressure

pain was elicited in three patients. The average duration of illness before admission was 43.5 days with a broad range (5 to 120).

Four of the seven patients had a fever (temperature greater than 38.3°C [101°F]) at presentation; two others became febrile during their hospital stay. One patient remained afebrile throughout his course. Physical findings consistent with pleural effusion or pneumonia, or both, were noted in every case. On abdominal examination two patients were found to have upper abdominal tenderness. The liver was not thought to be enlarged in any of the seven cases. All of the patients had leukocytosis with a mean leukocyte count of 16,900 per μl (range, 11,200 to 20,000). Liver function tests showed minimal abnormalities in six patients and essentially no abnormalities in the seventh. Liver scans showed a solitary right lobe defect in six patients. In the seventh patient, an abdominal computed tomographic (CT) scan showed a large, left upper quadrant abscess contiguous with the liver. All seven patients had antibody to amebic antigens detected by counterimmunoelectrophoresis (CIE).

In the seven patients there was a total of 12 pleuropulmonary complications (Table 1). These included three cases of inflammatory pleural reaction with effusion; two episodes of rupture into the pleural space with empyema, and seven episodes of rupture into the airways resulting in consolidation (two), abscess (three) and hepatobronchial fistula (two). In two patients, the diagnosis of amebiasis was made only after an exploratory operation. All seven patients responded promptly to treatment with metronidazole and were asymptomatic at the time of discharge. Three illustrative cases are presented below.

Reports of Cases

Case 1. Reactive Pleural Effusion

Three months before the present admission this 42-year-old Mexican man (patient 1, Table 1) was evaluated for chest pain and found to have a left-sided pleural effusion. Diagnostic thoracentesis showed an exudative fluid that was sterile and contained no tumor cells. A presumptive diagnosis of tuberculosis was made and isoniazid and rifampin therapy was begun. On this therapy his symptoms worsened and he was readmitted to hospital with chest pain and fever. The peripheral leukocyte count was 17,800 per μl, the serum alkaline phosphatase was 151 IU per liter and the albumin was 3.0 grams per dl. Other liver function studies did not show abnormalities. The chest roentgenogram showed a left pleural effusion and an elevated hemidiaphragm. An abdominal CT scan showed a left subphrenic abscess contiguous with the left lobe of the liver. The pleural effusion was again sterile and contained 5.9 grams per dl protein, 79 IU per liter lactic dehydrogenase (LDH) and 4,600 leukocytes per μl, of which 30% were polymorphonuclear leukocytes. The diagnosis of amebiasis was not considered.

On exploratory laparotomy a large left upper quadrant abscess was found and drained. *Entamoeba histolytica* was seen in the aspirated material and metronidazole, 750 mg, was initially given parenterally every eight hours for two days and orally thereafter. Additionally, both Gram-nega-

TABLE 1.—*Clinical, Laboratory and Therapeutic Data on Patients With Pleuropulmonary Amebiasis*

Patient	*Age,Sex*	*Chief Complaint*	*Other Complaints*	*Bilirubin* mg/dl*	*AST* IU/liter*	*ALT* IU/liter*	*Alk Phos* IU/liter*	*Chest X-ray*	*Abdominal Scan*	*Pleuropulmonary Complication(s)*	*Treatment*
1	42 ♂	Left chest pain	LUQ pain, Fever	0.4	13	29	151	Left pleural effusion; elevated left diaphragm	CT: left subphrenic abscess contiguous with liver	Reactive pleural effusion	Exploratory laparotomy, metronidazole
2	27 ♀	Right chest pain	Dyspnea	0.4	56	78	. . .	Opacified right lung	Liver scan: cold defect	Empyema	Tube thoracostomy, metronidazole
3	70 ♀	Right chest pain	RUQ pain, Anorexia, Weight loss	0.5	13	9	130	Loculated right pleural effusion	Liver scan: cold defect	Empyema	Tube thoracostomy, metronidazole
4	27 ♂	Hemoptysis	Fever Weight loss, Night sweats	0.2	17	22	101	LLL infiltrate	Liver scan: cold defect	Consolidation, hepatobronchial fistula	LLL lobectomy, metronidazole
5	21 ♂	Persistent cough	RUQ pain, Anorexia	0.4	66	118	302	Air fluid level RLL, pleural thickening	Liver scan: cold defect	Lung abscess	Metronidazole
6	41 ♂	Chocolate sputum	None	0.6	19	25	231	RLL cavity, right pleural effusion	Liver scan: cold defect	Lung abscess, hepatobronchial fistula, reactive pleural effusion	Metronidazole
7	45 ♂	Dyspnea	None	2.0	162	63	159	RLL/RML cavity and infiltrate, right pleural effusion	Liver scan: cold defect	Lung abscess, consolidation, reactive pleural effusion	Metronidazole

LUQ = left upper quadrant, CT = computed tomography, RUQ = right upper quadrant, LLL = left lower lobe, RLL = right lower lobe, RML = right middle lobe

*Normal values: bilirubin, 0 to 1.1 mg/dl; AST = aspartate aminotransferase (or, glutamic oxaloacetic transaminase), 7 to 40 IU/liter; ALT = alanine aminotransferase (or, glutamic pyruvic transaminase), 7 to 40 IU/liter; Alk Phos = alkaline phosphatase, 30 to 115 IU/liter.

tive and Gram-positive organisms were noted and treatment with tobramycin and ticarcillin disodium was begun. Subsequent cultures grew *Escherichia coli* and three species of *Bacteroides*. Counterimmunoelectrophoresis showed serum antibodies to *E histolytica*. The patient's condition improved within 48 hours after therapy was initiated. The left pleural effusion resolved and he was discharged without symptoms 24 days later.

Case 2. Amebic Rupture into the Pleural Space

The patient, a 27-year-old Mexican woman (patient 2), had resided in the United States for 12 months when she was admitted to hospital with a two-day history of severe, right-sided pleuritic chest pain and dyspnea. On admission her temperature was 38.5°C (101.3°F) and on physical examination she had findings of a right-sided pleural effusion. The abdominal examination showed no abnormalities. Laboratory studies showed a leukocyte count of 18,000 per μl and minimally abnormal liver function. Arterial blood gases done with the patient breathing room air showed a pH of 7.47, partial carbon dioxide pressure (Pco_2) 30.5 mm of mercury and partial oxygen pressure (Po_2) 54 mm of mercury. A chest roentgenogram showed opacification of the right lower hemithorax.

The initial diagnosis was pneumonia or pulmonary embolism and she was treated with penicillin and heparin. The next day the entire right lung field was opacified. A diagnostic thoracentesis showed chocolate-colored purulent material with a protein of 4.0 grams per dl, LDH 3,340 IU per liter, glucose 93 mg per dl and amylase 55 mg per dl. This material contained no bacteria on direct examination or culture. The serum was strongly positive for antibodies to *E histolytica* by CIE. On ultrasonography there was an 8.6 by 11 cm filling defect in the right posterior lobe of the liver. Administration of metronidazole, 750 mg by mouth every eight hours, was begun and a right tube thoracostomy drained 860 ml of purulent material. The patient's symptoms resolved over 36 hours, and she was discharged with a chest tube in place. Two months later she underwent decortication for an entrapped lung. Nine weeks thereafter she was asymptomatic and the chest roentgenogram showed minimal fibrotic changes. Ultrasonography showed that the abscess cavity in the liver had resolved.

Case 3. Amebic Rupture Into the Bronchial Airways

The patient, a 27-year-old Mexican man (patient 4), was admitted to hospital after four months of intermittent hemoptysis, fever, night sweats and a weight loss of 9 kg (20 lb). He had no abdominal pain or diarrhea. His temperature was 38.7°C (101.7°F) and he had dullness to percussion and rales in the left base. Laboratory studies showed a leukocyte count of 19,300 per μl and normal liver function. Chest x-ray films showed a left lower lobe infiltrate with consolidation (Figure 1). Sputum cultures yielded no pathogenic bacteria and bronchoscopy was negative. A diagnosis of tuberculosis was made and treatment with isoniazid and rifampin was begun. The hemoptysis and fever persisted and he underwent a left lower lobectomy. Surgical exploration showed an abscess with a sinus tract leading to the right lobe of the liver. *Entamoeba histolytica* was found in the resected tissue.

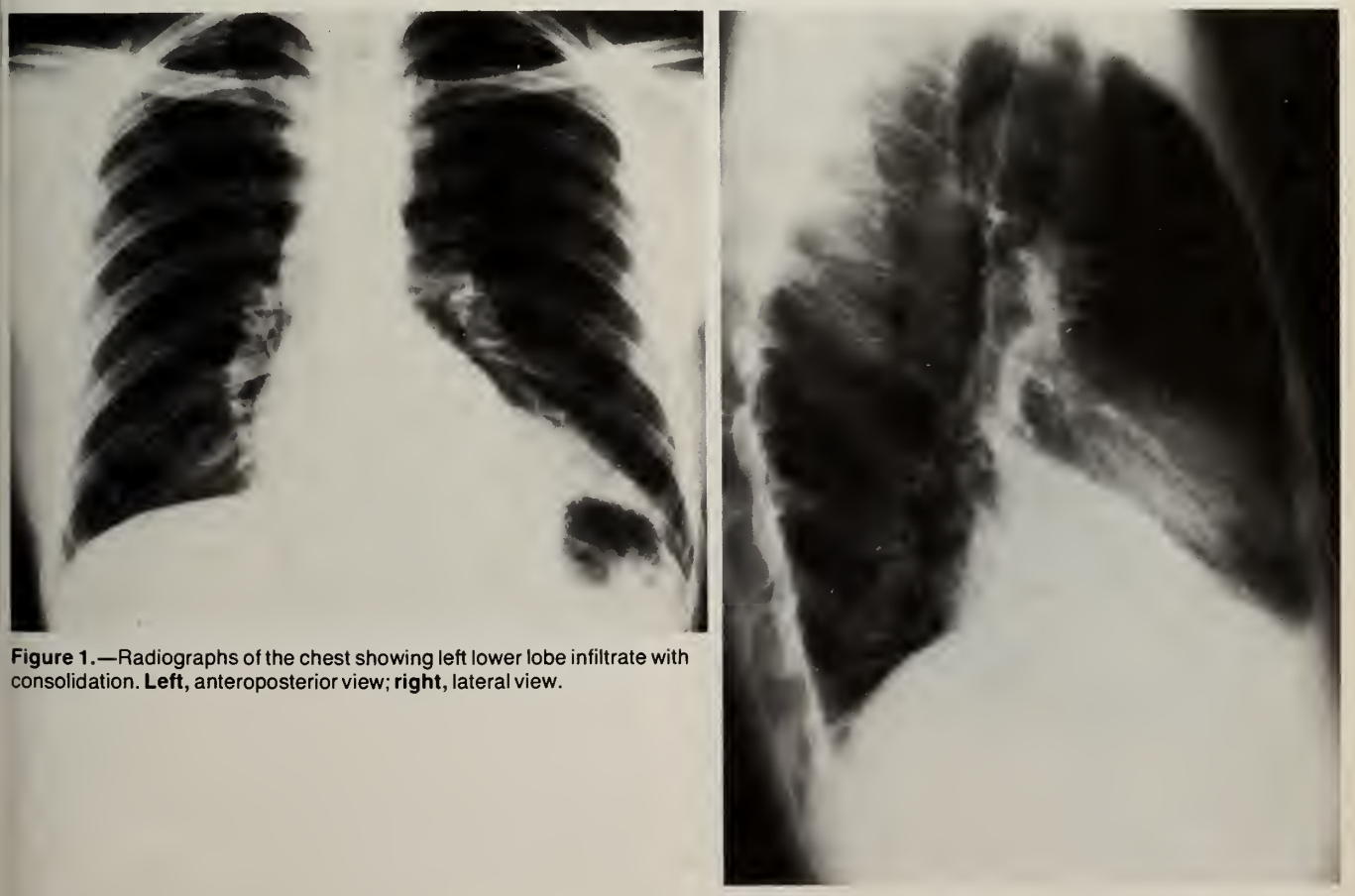

Figure 1.—Radiographs of the chest showing left lower lobe infiltrate with consolidation. **Left,** anteroposterior view; **right,** lateral view.

After the surgical procedure, CIE showed serum antibodies to *E histolytica*. On ultrasonography (Figure 2) and a liver-spleen scan, a single abscess was found in the right lobe of the liver. Metronidazole, 750 mg, was given orally every eight hours with prompt improvement. He was discharged without symptoms 14 days later. Two months later the patient was still healthy, although an ultrasound examination and liver-spleen scan showed a residual hepatic defect.

Discussion

Our seven patients had symptoms that were typical of the previously reported pleuropulmonary complications of amebiasis.[2,4,5] The prodromal symptoms were insidious in onset. Complaints of abdominal pain, weakness, weight loss and anorexia were vague and were elicited only in retrospect after the correct diagnosis had been established. The major symptoms were referable to the thorax. These included shortness of breath, cough and pleuritic chest pain. Whereas the onset of symptoms in some patients suggested an acute inflammatory process, in others the insidious nature of the symptoms was more suggestive of a chronic wasting disease. The diagnosis of tuberculosis was frequently suggested both because of the symptoms and because the patients came from areas where there tended to be a high incidence of endemic tuberculosis. Physical findings similarly pointed to intrathoracic disease. It is important to emphasize that the liver was not enlarged in any of our patients, tenderness over the liver was absent and laboratory studies showed such minimal abnormalities that the liver was not thought to be involved.

Three kinds of pleuropulmonary involvement can be distinguished in association with liver abscess, and in any individual patient there may be a progression of one complication to another. About a third of cases of pleuropulmonary amebic disease have an exudative, reactive pleural effusion, reflecting the presence of infection immediately below the diaphragm (patient 1).[1] Symptoms include cough and pleuritic chest pain, occasionally with radiation to the shoulder.[1,3,4,6] Radiographic findings of atelectasis or reactive pneumonitis may be present.[2] In the remaining two thirds of patients with pleuropulmonary disease, a hepatic abscess actually erodes into the pleural space (33% of cases), the lung parenchyma (56%) or both (12%).[1] (A third outcome, which is outside the scope of this article, is rupture into the pericardium, especially in disease involving the left lobe of the liver.[6])

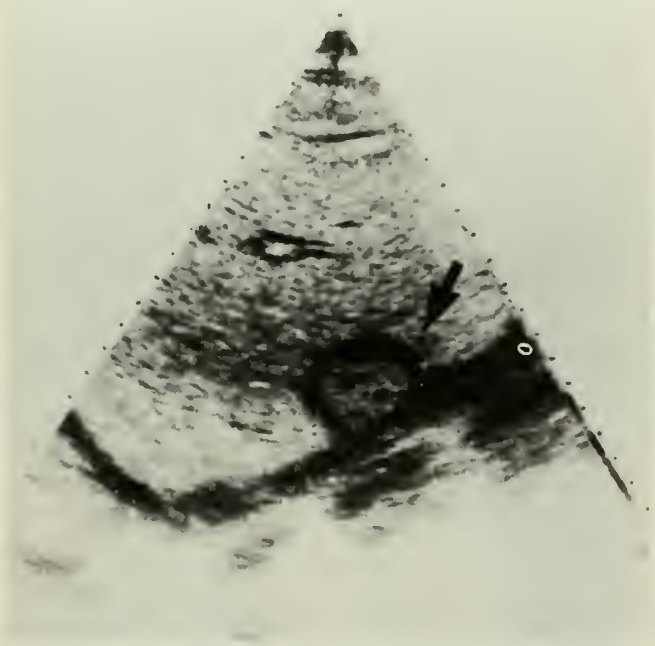

Figure 2.—Longitudinal view of a solitary amebic abscess **(arrow)** on liver ultrasonography.

Rupture into the pleural space is signaled by an abrupt worsening of pleuritic chest pain and shortness of breath (patient 2). On occasion, respiratory distress and even shock may ensue.[7] A roentgenogram of the chest may show a massive pleural effusion, occasionally with mediastinal shift.[7] The pleural fluid may be purulent or it may be greenish or dark brown, reflecting the presence of bile or digested liver tissue; amebae are detected in less than 10% of cases.[1,7]

Erosion directly into the lung parenchyma may occur with little involvement of the pleural space (patient 5). Most frequently this involves the right lower and middle lobes.[1] Rupture into a bronchus causes a dramatic clinical event with expectoration of dark-colored debris. Intense microscopic examination may show amebae, but only in a small proportion of cases.[4] A hepatobronchial fistula may lead to natural drainage of the liver abscess; alternatively, intrabronchial spread of this material may result in respiratory insufficiency.[6] Chest roentgenograms show consolidation or abscess, often with a distinctive tenting of the diaphragm,[1,3,4] sometimes called the Mexican hat sign.[1] The possibility that amebae might reach the lung via a hematogenous route[2-4] arose because intrathoracic disease was identified in some patients who did not have apparent liver involvement. The use of currently available techniques shows liver disease to be present in the vast majority of cases of intrathoracic amebiasis[1]; nevertheless, the possibility of hematogenous dissemination is supported by the rare occurrence of amebic brain abscess.[6,8]

Early misdiagnosis of amebic infections involving the pleura and lung occurs chiefly because the possibility is not considered. High-risk groups include travelers and immigrants from endemic areas (especially Mexico). Future studies may help elucidate whether homosexual men, who appear to have high rates of enteric protozoal infection,[9-11] are also at increased risk. A history of diarrheal disease, which is linked to amebic infection in the minds of most physicians, is absent in half of the patients.[2] Jaundice is unusual,[12] and hepatic function is normal or only mildly abnormal, further directing attention away from the liver.

Once the diagnosis of pleuropulmonary amebiasis is considered, further evaluation depends somewhat on the clinical presentation. If diarrhea is present, a proctoscopic examination may show changes consistent with amebiasis and the feces may contain amebic trophozoites or cysts. Sputum and pleural fluid, if present, should be closely evaluated for amebae despite the relatively low yield. Ultrasonography, liver scan or a CT scan is expected to show a liver abscess. A serum specimen should be sent for either indirect hemagglutination titers or amebic antibodies by CIE to confirm the diagnostic impression; antibody is detected in almost all patients who have invasive amebic disease and only rarely in those without parenchymal infection.

Our seven patients received metronidazole, 750 mg

every eight hours, and two of these also underwent surgical drainage; all were cured. There is some controversy over the need to use emetine hydrochoride or dehydroemetine in addition to metronidazole. Those investigators with the greatest clinical experience currently recommend that both drugs be used,[1] presumably because the success rate with one drug alone was insufficient; their data do not, however, fully support this conclusion. Others recommend the use of metronidazole alone.[6] As a result, Jones[12] concludes that metronidazole should be given together with a two- to three-day course of emetine. If extension of an amebic abscess of the liver into the chest causes acute illness, therapy with both metronidazole and emetine should be administered parenterally. The use of iodoquinol (diiodohydroxyquin) is recommended by some authorities[12] to eradicate luminal cysts, though the need to treat asymptomatic subjects who are carrying amebic cysts in their colon is open to question.

The reactive inflammatory pleuropulmonary complications respond well to treatment with amebicidal drugs, though it seems prudent to drain large effusions at the time of diagnostic thoracentesis to prevent respiratory compromise. The overall mortality of reactive pleural disease due to amebiasis was 2.5% in a large series of cases reported from Mexico.[1] Rupture into the pleural cavity with resulting amebic empyema carries a higher mortality (14.2%) and requires more aggressive therapy.[1] In addition to the administration of metronidazole, the pleural cavity must be drained by a large-bore tube to ensure adequate removal of necrotic tissue.[1,7] Rupture of the abscess into the airways may necessitate intensive respiratory support; however, with the spontaneous drainage, most patients improve on medical therapy alone.[1]

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Influence of Perfusion and Ventilation Scans on Therapeutic Decision Making and Outcome in Cases of Possible Embolism

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We examined the influence of perfusion (Q) and ventilation (V) scans on therapeutic decision making and outcome among 229 patients referred for lung scans because embolism was suggested and found that specific V/Q scan patterns strongly influenced postscan decisions regarding initiation, maintenance or cessation of heparin therapy. These therapeutic decisions bore a relationship to outcome (recurrences and death) and disclosed decision-making deficits that need remedy by future investigational and educational efforts.

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In patients suspected of having pulmonary embolism, perfusion (Q) and ventilation (V) lung scans are frequently done. However, there has been no systematic evaluation of how scan results influence therapeutic decision making or relate to patient outcomes.

We have examined these issues in a retrospective analysis of 229 cases of patients with possible embolism referred to the University of California, San Diego (UCSD), Nuclear Medicine Department for perfusion scans during a one-year period. The results indicate that, at our institution, specific scan patterns do influence decision making and also relate to patient outcome in terms of thromboembolic recurrence and death due to embolism.

Patients and Methods

The hospital records of all patients referred for perfusion lung scanning to rule out pulmonary embolism at the UCSD Medical Center during 1979 were reviewed. There were 236 such patients, 7 of whom had a pulmonary angiogram and were excluded from further analysis. In the remaining 229 patients, admission diagnoses, risk factors, signs and symptoms and laboratory data that antedated the request for lung scanning were recorded. All perfusion scans included four views (anterior, posterior and both laterals) and most included six views (both posterior obliques). Patients received about 2 mCi of macroaggregates labeled with technetium 99m, and imaging was done with a large-field-of-view gamma camera (Picker 4/15) centered over the 140 keV photopeak and using a 20% window with a high-resolution, low-energy, parallel-hole collimator.

Physicians in nuclear medicine decided, after review of the Q scan and a chest x-ray film, whether or not a ventilation scan was warranted. If warranted, ventilation scans were done immediately after perfusion imaging.[1] They consisted of a wash-in phase during tidal breathing, an equilibrium image and a seven-minute wash-out phase. The same camera was used, employing a 15% window centered on the 81-keV photopeak.

Patients were placed into five subgroups according to the original perfusion scan report (Table 1): (1) perfusion scan showing no abnormalities, (2) Q scan defect(s) limited to area(s) of chest film abnormality, (3) single subsegmental defects, (4) multiple subsegmental defects and (5) single or multiple segmental (or larger) defects. If more than one type of defect was present, the scan was categorized according to the largest defect reported. A chest x-ray film was taken in all patients within 24 hours of—usually just before—the lung scan. All lung scans and chest films were also reviewed independently by two of us (A.J.M. and M.S.K.). Disagreements with the original report, or between reviewers, occurred in only four instances. However, all scan results were classified according to the original report provided. In all, 51 of the

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perfusion scans (22%) showed no abnormalities. About half of these patients had been started on heparin therapy before the scan; none received heparin after the scan unless venous thrombosis was diagnosed. The very low rates of recurrence and death due to embolism in this group have been reported in detail elsewhere,[2] and this group will not be further discussed.

Patient follow-up in the remaining groups was achieved by reviewing all inpatient and outpatient records subsequent to the index scan. All patients were followed by faculty or house officers of the Department of Medicine. If records disclosed no subsequent patient visit for at least a month after discharge, an effort was made to contact the patient directly. If this effort failed, the patient was placed in the "no follow-up" category.

Three therapeutic decisions made by the attending physicians during the index admission were examined: the prescan decision regarding anticoagulant use, the postscan decision and the decision to maintain anticoagulant therapy following discharge.

With respect to outcome, we analyzed the frequency of thromboembolic recurrence and of death due to embolism during the index admission and during follow-up. The criteria used to define both recurrence of venous thrombosis or embolism and death due to embolism were as follows:

- *Thromboembolic recurrence.* This was diagnosed if, after the initial lung scan, either of the following criteria was met: the results of a specific diagnostic test indicated recurrence of pulmonary embolism (lung scan or pulmonary angiogram) or deep venous thrombosis (venogram, impedance plethysmography or radiofibrinogen leg scan); a thromboembolic recurrence was entertained clinically by the attending physicians and led to extension of the index admission, a subsequent hospital admission or initiation of anticoagulant therapy. Unless a definitive study ruled out a recurrence, all such patients were counted as having a recurrence.
- *Death due to embolism.* Death was attributed to embolism when (1) autopsy was done and disclosed pulmonary emboli, *or* (2) autopsy was not done, but a clinical diagnosis of embolism was considered the cause of death, *or* anticoagulant therapy was applied during final admission because of a diagnosis of embolism *or* a scan or pulmonary angiogram documented embolic recurrence. Statistical analyses were done using the Fisher's exact test.

Results

The distribution of the 229 patients among the lung perfusion scanning subgroups is shown in Table 1. Ventilation scans were done in 120 instances (52%) (Table 1). Those 109 patients in whom nuclear medicine physicians decided not to do a ventilation study fell into one of four categories: (1) a perfusion scan showed no abnormalities (50), (2) their perfusion scan defects exclusively matched chest film abnormalities (25), (3) perfusion scan defects were considered too small (subsegmental) to resolve with xenon 133 (29) and (4) those with segmental or larger defects who were too ill to cooperate for a ventilation study (5).

Patient Risk Profiles

The patient risk profiles in the three major scan subgroups analyzed are presented in Table 2. Patients in each subgroup had significant risk factors for thromboembolism.[3-12] No statistically significant differences ($P < .05$) were noted among the groups for coexistent disease states, age, sex or race, presenting symptoms, signs or arterial blood gas analysis (not listed). This was true whether patients with segmental or larger defects were analyzed as one group or, as in Table 2, according to ventilation match or mismatch.

Decision Making and Outcome in Subgroups

Single subsegmental defects. Only ten patients had single subsegmental defects. Ventilation scans were done in six and five showed V/Q match. In three patients, heparin had been initiated before the ventilation scan and, in all, therapy was discontinued after the scan. Thus, no patient received heparin after a scan. No recurrences or deaths occurred in this group of patients during admission or during an average of seven months of follow-up.

Perfusion scan defects matched by chest film findings. Of the 31 patients in this category, 6 had a ventilation scan. In all, the ventilation defect(s) "matched" perfusion defect(s).

Seven patients had been started on heparin therapy before the scan (Table 3). After the scan, heparin therapy was continued in three of these and initiated in none. Thus, 28 patients received no anticoagulants following lung scanning.

During the index admission, there were no recurrences of thromboembolism. Four patients died during admission, none due to embolism according to the criteria described;

TABLE 1.—*Perfusion Scans Classified by Category, Showing Scan Results in Terms of Ventilation/Perfusion (V/Q) Matching*

*Perfusion (Q) Scan Pattern**	*Number*	*Ventilation (V) Scan Done Number (Percent)*	*V/Q Match Number*	*V/Q Mismatch Number (Percent)*
Q normal	51	1 (2)	1	0 (0)
Q single SS	10	6 (60)	5	1 (17)
Q matches CXR	31	6 (19)	6	0 (0)
Q multiple SS	85	60 (71)	60	0 (0)
Q segmental	52	47 (90)	17	30 (64)
TOTAL	229	120 (52)	89	31

*Categories: Q normal = no abnormalities found on perfusion scan; Q single SS = a subsegmental defect found on perfusion scan; Q matches CXR = defect(s) on perfusion scan limited to area(s) of chest roentgenographic abnormality; Q multiple SS = subsegmental defects found on perfusion scan; Q segmental = segmental or larger defect(s).

TABLE 2.—*Patient Profiles in Three Perfusion Scan (Q) Subgroups**

Patients	*Q Matches CXR*	*Q Multiple Subsegmental*	*Q segmental*	
			V Match-V Mismatch	
Number	31	85	17	30
Average age, years	49	59	49.6	50.9
M/F	1.1/1	1.2/1	1.4/1	1.7/1
Risk Factors†	*Number (Percent)*	*Number (Percent)*	*Number (Percent)*	*Number (Percent)*
Smoker/COPD	11 (35)	62 (73)	12 (71)	18 (60)
Heart disease	13 (42)	42 (49)	5 (29)	8 (27)
Cancer	11 (35)	9 (11)	2 (12)	12 (40)
Immobilization	10 (32)	13 (15)	5 (29)	9 (30)
Postoperation	7 (23)	5 (6)	0 (0)	6 (20)
Hx DVT/PE	0 (0)	5 (6)	0 (0)	3 (10)
BCP/estrogens	2 (6)	2 (2)	3 (18)	4 (13)

*Defect(s) on perfusion scan matches region(s) of chest roentgenographic infiltrate; multiple subsegmental defects; or segmental defects with ventilation scan (V) match or mismatch.

†COPD = chronic obstructive pulmonary disease; Hx DVT/PE = history of deep venous thrombosis or pulmonary embolism, or both; BCP/estrogens = recent (within prior 3 months) use of oral birth control medication or estrogens.

none were receiving anticoagulants. Three patients were discharged on a regimen of long-term anticoagulation.

Of the 27 patients discharged, 24 (89%) were followed for an average of seven months (Table 4). One subsequent documented (by angiogram) embolic event occurred (4%). This patient had received heparin therapy for ten days during his index admission three months before. There were four deaths during follow-up; none was attributed to embolism; one patient was receiving anticoagulant therapy long-term.

Multiple subsegmental defects. There were 85 patients in this subgroup; 60 of these patients had a ventilation scan, all showing V/Q "match" (Table 1).

Heparin therapy had been started before the scan in 25 of these patients (29%) (Table 3). Following the lung scan, heparin therapy was discontinued in 11 patients and not initiated in any. Thus, only 14 patients (16%) were maintained on heparin therapy after the scan.

During the index admission, there was one recurrence, of pulmonary embolism, in a patient four days after completion of a ten-day course of heparin. He was re-treated and discharged. There were three deaths during admission; none was attributed to embolism; two of the patients were receiving heparin when death occurred. Postmortem examination in two, one receiving heparin and one not, disclosed no emboli.

Eighteen patients were discharged on long-term anticoagulant therapy, even though only 14 of these had been treated with heparin after a perfusion scan. The other four patients were felt to have risk factors at discharge warranting such therapy.

Of the 82 patients discharged, 78 (95%) were followed for an average of eight months (Table 4). There were no recurrences. Five patients died during the follow-up period, three of whom were receiving anticoagulant therapy. None of the deaths was attributable to embolism.

Segmental defects. Of 52 patients whose perfusion scans showed at least one segmental or greater defect, 47 (90%) had a ventilation study (Table 1); 17 of these patients had V/Q mismatch.

Of the 17 with a segmental V/Q match pattern, 6 had been started on heparin therapy before the scan (Table 3). The heparin regimen was stopped after the scan in three of these patients and initiated in none. Thus, only three of these patients (18%) received postscan heparin. There were no recurrences during admission. There was one death, not attributed to pulmonary embolism, in a patient receiving heparin. No patient was discharged on a regimen of long-term anticoagulation. Of the 16 patients who survived the index admission, 15 (94%) were followed for a period averaging nine months (Table 4). There were no episodes of subsequent embolism. One died of nonembolic causes.

Among the 30 patients with a segmental V/Q mismatch pattern, 15 (50%) had been started on heparin therapy before the scan. This was continued in all after the scan. Of the remaining 15, heparin therapy was initiated after the perfusion scan in 13 and 2 were not treated because the emboli were septic. Thus, all patients except those with septic emboli received heparin after the scan.

There were three embolic recurrences during admission despite heparin treatment: two were documented by new segmental V/Q "mismatch" zones; one was a paradoxic embolus to the brachial artery in a patient with venous thrombosis and a patent foramen ovale. Three patients died during the index admission; all deaths were attributed to embolism; all were receiving heparin; one postmortem examination was done and documented emboli. In all, 16 patients (59%) were discharged on long-term anticoagulation. The 11 patients not given anticoagulant therapy after discharge included 2 who had septic emboli; the rationale for anticoagulant cessation in the other 9 was not apparent.

Of the 27 patients surviving the index admission, 26 (96%) were followed for a period averaging nine months. Six patients had thromboembolic recurrences: one with documented venous thrombosis, the five others with clinically diagnosed embolism. Of these six, three were receiving anticoagulants at recurrence and three were not. Four patients died during follow-up; three deaths were attributed to embolism. Two were receiving anticoagulant therapy at the time of death; in one, heparin therapy was withheld because of a hemorrhagic cerebrovascular accident. One postmortem examination was done and disclosed pulmonary emboli.

Of the five patients with segmental or larger perfusion defects who had no ventilation scan, three had been started on heparin therapy prescan. Two were maintained on heparin therapy after the scan. There were no recurrences during admission. One death, not attributed to embolism, occurred. No patient was discharged on anticoagulant therapy. The four surviving patients were followed an average of eight months. There were no recurrences or deaths.

TABLE 3.—*Decisions and Events During Index Admission of Patients in Whom Defects Found on Perfusion Scan (Q) (N = 168)*

*Perfusion Scan Pattern**	*Patients Number*	*Anticoagulation Therapy*		*Outcome*		*Discharged on Anticoag Regimen*
		Heparin Prescan Number (Percent)	*Heparin Postscan Number (Percent)*	*Recurrence Number*	*Deaths/PE/Autopsy†*	
Q matches CXR . .	31	7 (23)	3 (10)	0	4/0/0	3/27
Q multiple SS . . .	85	25 (29)	14 (16)	1	3/0/2	18/82
Q segmental	52					
V match	17	6 (35)	3 (18)	0	1/0/0	0/16
V mismatch . . .	30	15 (50)	28 (93)	3	3/3/1	16/27
No V	5	3 (60)	2 (40)	0	1/0/0	0/4

Anticoag = anticoagulation

*Q matches CXR = defect(s) on perfusion scan limited to area(s) of chest roentgenographic abnormalities; Q multiple SS = multiple subsegmental defects on perfusion scan; Q segmental = segmental or larger defects on perfusion scan, in which case a ventilation scan (V) was likely to have been done.

†Total No. deaths/No. attributed to pulmonary embolism/No. autopsies.

TABLE 4.—*Outcome of Patients (N = 156) During Follow-up Period*

*Perfusion Scan Patterns**	*Available† Number*	*Follow-up‡ Number (Percent)*	*Average Duration of Follow-up Months*	*Recurrence*		*Deaths/PE/Autopsy§*
				PE	*DVT*	
Q matches CXR . .	27	24 (89)	7	1		4/0/0
Q multiple SS . . .	82	78 (95)	8	0	0	5/0/0
Q segmental	47					
V match	16	15 (94)	9	0	0	1/0/0
V mismatch . . .	27	26 (96)	9	5	1	4/3/1
No V	4	4 (100)	8	0	0	0/0/0

PE = pulmonary embolism, DVT = deep venous thrombosis

*See Table 3 for explanation of perfusion scan (Q) and ventilation scan (V) pattern.

†No. surviving index admission.

‡Patients followed for one month or more.

§Total No. deaths/No. attributed to pulmonary embolism/No. autopsies.

The incidence of thromboembolic recurrence during admission and follow-up (Tables 3 and 4) was significantly higher among patients with segmental V/Q mismatch than among those with segmental V/Q match ($P < .05$), those with multiple subsegmental defects ($P < .001$) and those who had perfusion defects that matched the findings of the chest film ($P < .01$).

Venous studies. Among the scan groups analyzed in this report, in only 50/168 patients (30%) was the diagnosis of venous thrombosis pursued by impedance plethysmography, radiofibrinogen leg scanning or venography, or all of these (Table 5). The timing of leg studies vis-à-vis the lung scan was inconsistent; it ranged from a day or two before the scan to several days after the scan. When done, these tests appeared to influence therapeutic decision making. Of the three patients with perfusion defects matched to chest film defects who were maintained on heparin therapy after the scan and discharged on heparin therapy, all had positive leg studies. Of the 14 with multiple subsegmental defects maintained on heparin therapy after the scan, 8 had positive leg studies. Among those with segmental or larger perfusion scan defects mismatched by ventilation scan findings, leg studies were positive in 14 of the 16 discharged on a regimen of heparin.

The inconsistent timing and application of venous studies made more precise analyses of their influence on decisions or outcome impractical.

Discussion

Classical studies of diagnostic techniques for venous thromboembolism assess their sensitivity, specificity and reproducibility.[13-24] While such information is important, that was not our objective. Rather, we wished to assess the influence of lung scans on physician decision making and how these decisions conditioned patient outcome. Such assessments have not previously been reported.

Clearly, one cannot assess physician decision making if a protocol is in place that mandates such decisions. Furthermore, at the time of this study, there was no policy at our institution that mandated any of the decisions taken, nor was there an unstated, but generally accepted, philosophy. Our findings reflect the fact that there was nonuniformity in physician decision making regarding the following aspects of patient management: whether to do a ventilation scan, when heparin therapy should be initiated or discontinued, how such patients are best followed and how best to confirm the diagnosis of recurrence. Such nonuniformity is not condoned by the authors; it is merely reported. Despite the interpretive limitations that such variability imposes, our data indicate that perfusion and ventilation scan patterns do influence physician decision making and do relate to patient outcome.

The first therapeutic decision was whether to initiate heparin therapy on the basis of data available *before* the lung scan. Of the 168 patients, the decision was to initiate heparin therapy in 56 (33%).

The second decision was whether to maintain, initiate or discontinue administration of heparin after the scan. Among the 56 started on heparin therapy prescan, it was discontinued in 19 patients after the scan (34%). Considering that heparin therapy also was discontinued in virtually all of those in whom no abnormalities were found on a perfusion scan, it is clear that scans did influence decisions to discontinue heparin therapy. Furthermore, scan results also led to the initiation of heparin therapy in 13 patients who had not been given heparin before the scan.

Examination of the various scan subgroups indicates that these decision changes were not random but were conditioned by specific scan patterns. Among patients with perfusion scans showing defect(s) limited to area(s) of pulmonary infiltrates seen on chest film, heparin therapy was initiated in none and maintained in only three (all had venous thrombosis). The ventilation scan did not appear to influence these decisions. Likewise, among the 85 patients with a perfusion scan showing multiple subsegmental defects, heparin therapy was initiated after the scan in none and maintained in only 14 (8 with positive leg studies). Again, ventilation scans did not influence these decisions.

Among patients with segmental or larger perfusion defects, the ventilation scan did appear to influence postscan therapeutic decisions. Of the 17 with V/Q match, only three received heparin after the scan, one because of venous thrombosis. In sharp contrast, of the 30 patients with V/Q mismatch, 15 had heparin therapy continued and 13 had heparin therapy *initiated* following the scan. Indeed, the only two patients who did not receive heparin after the scan had septic emboli.

TABLE 5.—*Venous Studies Done in 168 Patients With Perfusion Scan Defects**

Perfusion Scan Pattern†	#	*Leg Studies* Number Done / Number Pos	*Postscan Heparin Therapy* Number/Pos Leg	*Discharged on Anticoag Regimen* Number/Pos Leg
Q matches CXR	31	10/6	3/3	3/3
Q multiple SS	85	13/9	14/8	18/5
Q segmental	52			
V match	17	3/1	3/1	0
V mismatch	30	21/14	28/14	16/14
No V	5	3/2	2/2	0
	168	50/32	50/28	37/22

Anticoag = anticoagulation

*Studies done were venography, impedance plethysmography or radiofibrinogen leg scan. Of 50 patients studied by one or more techniques, a positive (pos) result was found in 32. A majority of those continued on heparin post-scan and discharged on anticoagulants had positive leg studies.

†See Table 3 for explanation of perfusion (Q) and ventilation (V) scan patterns.

The next therapeutic decision—whether to maintain anticoagulant therapy after discharge—appeared to have been conditioned by the scan results (Tables 3 and 5), the detection of venous thrombosis and considerations of long-term thromboembolic risk. Of the 37 patients discharged on a regimen of anticoagulation, 24 (65%) had either a scan pattern showing segmental or larger perfusion defects with ventilation mismatch, test findings of venous thrombosis, or both. Why the other patients were continued on anticoagulant therapy is not evident from the record, nor did the record reflect why long-term anticoagulation was not given to some patients, such as nine who had segmental or larger perfusion defects and V/Q mismatch. It seems evident that our physicians do not use consistent criteria in making decisions about long-term anticoagulant therapy.

However, the data indicating that scan patterns did influence therapeutic decision making do not answer the critical question: were the decisions appropriate? Only analysis of patient outcome can address that question.

In this series, the incidence of recurrence and of death due to embolism were the two outcome criteria. Unfortunately, precise identification of these events is difficult, whether patients are studied prospectively or retrospectively, as was reflected in a recent prospective study.[23] Because episodes of embolism may be asymptomatic,[24] even the most rigorous clinical follow-up will detect only recurrences that induce symptoms. Without symptoms, patients will not seek attention nor will physicians intervene. Unfortunately, the alternative is a study design that would mandate frequent follow-up scans or pulmonary angiograms among asymptomatic patients over periods of months or years, a design that is difficult to justify. Similarly, with respect to death due to embolism, a 100% autopsy rate is certainly desirable, but not attainable. In this study, we dealt with these problems by defining recurrence and death due to embolism quite liberally.This may lead to inclusion of excessive recurrences and deaths, but such a "worst case" analysis seems most appropriate. Despite such limitations, the outcome data were instructive. During the index admission, the decision to provide heparin therapy to a minority of patients with scan patterns other than segmental or larger V/Q mismatch was associated with only one recurrence and no embolic deaths. We have previously reported similar results in patients in whom anticoagulant therapy was discontinued after a perfusion scan showed no abnormalities.[1] In contrast, recurrence and embolic deaths occurred during the index admission in some 10% of those with segmental or larger perfusion defects mismatched by ventilation scan.

Long-term follow-up provided similar results. Among the 121 patients followed in the groups other than those with segmental V/Q mismatch, there was only one recurrence (of pulmonary embolism) and no deaths attributable to embolism. Yet less than 20% of these patients received anticoagulant therapy after discharge. In contrast, of the 26 patients with V/Q mismatch followed after discharge, there were six recurrences and three deaths attributable to embolism (two while patients were receiving heparin).

Whereas these outcome data suggest that the decisions regarding heparin therapy were generally appropriate, they leave several important questions unresolved. For example, physicians apparently concluded that a perfusion scan showing multiple subsegmental defects excluded embolism and, therefore, that anticoagulant therapy was not necessary. The acceptable outcome data do not validate such conclusions. The acceptable outcome could mean that, whereas an unknown percentage had small emboli, such small emboli, even if recurrent, do not cause significant symptoms or result in death. Indeed, the recent report by Hull and colleagues[23] favors the latter conclusion. Although their study differed substantially in design, they found that the pulmonary angiogram disclosed pulmonary emboli in 27% of patients with subsegmental defects and 17% with perfusion scan defects matched by chest film findings, versus 86% with segmental or larger defects mismatched by ventilation scan. Thus, clearly, emboli do occur in these other scan subgroups. However, the outcome data in the series of Hull and co-workers also reflect, as we found, a low risk of subsequent recurrences and deaths. Of their 139 patients with abnormalities seen on perfusion scans, most received no anticoagulant therapy because, by design, a combination of a negative pulmonary angiogram and a negative venogram led to withholding of therapy. An unknown number received anticoagulant therapy after discharge. Yet, these workers found only three documented recurrences during a one-year follow-up: one embolic event and two instances of venous thrombosis. The one embolic recurrence occurred in a patient with a segmental V/Q mismatch scan pattern. Further, of 25 deaths during follow-up, they attributed only 3 to embolism, 1 each in the segmental V/Q mismatch, subsegmental and chest film-matched groups.

Thus, while our report and that of Hull and co-workers cannot be directly compared, it is evident that the outcome data in both studies suggest that recurrence of, and death due to, embolism is quite uncommon among patients whose index scans show subsegmental or roentgenogram matching patterns. Further data bearing on this point are needed.

Likewise, the uniform decision to treat patients who had segmental or larger defects with V/Q mismatching does not indicate that such patients had emboli. That this type of V/Q mismatch is commonly associated with embolism is strongly suggested by other studies in which angiographic-scan comparisons have been made in selected patient groups.[15-19,23] As noted, the report of Hull and associates places this figure at 86%. The high recurrence or death rates (or both) we observed add further weight to the diagnostic implications of this scan pattern.

Another question that is stimulated, rather than resolved, by our observations is why studies for venous thrombosis were used so inconsistently in making initial and discharge decisions regarding anticoagulant therapy. Impedance plethysmography, radiofibrinogen leg scans and Doppler and contrast venography are all readily available at our institution. Yet, these studies were done in only a minority of these patients, even though most emboli come from lower extremity venous thrombosis.[20-25] Obviously, additional educational efforts are needed to emphasize the value of venous studies among patients in whom embolism is suggested.

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Cancer Incidence Among Employees of the Lawrence Livermore National Laboratory, 1969-1980

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The cancer incidence from 1969 through 1980 among active members of an occupational cohort (the Lawrence Livermore National Laboratory [LLNL]) was compared with that of the same-age sector of the total population of the San Francisco-Oakland Standard Metropolitan Statistical Area. Excesses were found for malignant melanoma of the skin and salivary gland tumors and a deficit for lung cancer in men. No excesses were noted for radiosensitive tissue groups. The overall incidence of cancer among LLNL employees for this time period is approximately that for the general population.

(Reynolds P, Austin DF: Cancer incidence among employees of the Lawrence Livermore National Laboratory, 1969-1980. West J Med 1985 Feb; 142:214-218)

An earlier study established that a fourfold excess incidence of malignant melanoma of the skin occurred among employees of the Lawrence Livermore National Laboratory (LLNL) between 1972 and 1977.[1] The LLNL is a high-technology, high-energy physics research facility in Alameda County, California. This study was undertaken to establish whether or not there was an unusual occurrence for any other site of cancer in this occupational cohort.

This has not been designed to be a study of radiation and cancer, but because of public and professional interest in the etiologic significance that radiation may have in this very specialized work force, we have grouped cancer sites by radiosensitivity criteria. This may serve as an indirect indicator of any unusual patterns of radiation-induced tumors.

There are three major sources of epidemiologic information on radiosensitive sites of cancer: follow-up studies of Hiroshima and Nagasaki survivors, occupational mortality studies of radiologists and patient series of persons exposed to therapeutic sources of radiation (primarily those with tinea capitis, ankylosing spondylitis, tuberculosis and thyroid disease).[2-4] There have also been a few mortality studies of radiation workers.[5-8] Interpretation of these data is complex because the probable carcinogenic effects of radiation are thought to be both a function of tissue-specific responses to the source and dosage of radiation and of host factors such as age and sex. There is a high level of agreement that human leukemia (excluding chronic lymphocytic leukemia) and cancers of the thyroid and bone marrow can be induced by a variety of radiation sources. The evidence is less clear for other sites of cancer, but tissues of the lung and female breast appear to be moderately radiosensitive.

Our study was designed to compare the incidence of all sites of cancer among active LLNL employees with that expected in the same age/sex population of the San Francisco-Oakland Standard Metropolitan Statistical Area (SMSA). We have also considered the LLNL cancer experience in three broad cancer categories (high, medium and low) of risk associated with ionizing radiation.

Subjects and Methods

The study cohort consisted of all active 1969-1980 LLNL employees between the ages of 20 and 69 years who resided in the San Francisco-Oakland SMSA. Person-years of observation were computed for the 12-year period by summing the annual distribution of eligible employee months by sex and 5-year age groups. No minimum period of employment was required to be included in the population at risk. The period of observation was limited to the period of active employment at the LLNL and ended with termination of employment or December 31, 1980, whichever came first. Total person-years of observation are listed in Table 1.

For this study, "observed" cases of cancer were tabulated only for employees whose date of diagnosis was concurrent with active employment at the LLNL and whose residence was within the Resource for Cancer Epidemiology (RCE) case ascertainment area. Cancer diagnoses (observed num-

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ABBREVIATIONS USED IN TEXT
LLNL = Lawrence Livermore National Laboratory
RCE = Resource for Cancer Epidemiology
SEER = Surveillance Epidemiology and End Results
SMSA = Standard Metropolitan Statistical Area

bers) were ascertained via automated record linkage between the annual LLNL employee files and the RCE's cancer incidence files for 1969 through 1980. The RCE has maintained a population-based registry for the San Francisco-Oakland SMSA since 1969 as part of the National Cancer Institute's Surveillance Epidemiology and End Results (SEER) Program and the Third National Cancer Survey. Ascertainment has been estimated to be 98% complete.[9] Hence, all new cases of cancer (excluding common nonmelanoma skin cancers) occurring among LLNL employees residing in the SEER surveillance area are likely to have been collected by the RCE.

The expected number of cancers for the study cohort was calculated by multiplying the 1973 to 1977 age- and sex-specific rates for the San Francisco-Oakland SMSA[10] for each site of cancer by the age- and sex-specific LLNL person-years of observation and summing across age groups. Published San Francisco-Oakland SMSA rates for 1973 through 1977 were chosen as representative of the total time interval 1969 through 1980 and as a practical alternative to costly new rate computations. A simpler procedure was used than that adopted for our earlier analysis of the incidence of malignant melanoma of the skin because there is less socioeconomic and environmental variation among other cancer sites. Also, because the rates during this time interval (except for melanoma and female lung and uterine cancer) appear to be stable, it was not as important to weight the comparison rates by temporal and residential patterns.

A total of 49 sites of invasive cancer and 11 sites of in situ cancer are reported here. For each site and sex an observed-to-expected ratio was computed. For each comparison ratio that exceeds the 95% confidence interval (for the ratio of an observed value of a Poisson variable to its expectation), as tabled by Bailar and Ederer,[11] significance indicators are reported. These values are not adjusted for multiple testing, as more than 100 comparisons were made. They are merely included as a relative scale for the observed differences.

TABLE 1.—*Lawrence Livermore National Laboratory Study: Total Person Years of Observation of San Francisco-Oakland SMSA Residents Only, 1969-1980*

Age Group Years	Person-Years		
	Men	Women	Totals
20-24	2,458.50	1,307.72	3,766.22
25-29	5,299.10	1,691.45	6,990.55
30-34	7,236.33	1,645.49	8,881.82
35-39	7,842.84	1,602.01	9,444.85
40-44	8,029.85	1,465.50	9,495.35
45-49	8,008.34	1,191.52	9,199.86
50-54	6,912.53	991.01	7,903.54
55-59	4,737.88	697.56	5,435.44
60-64	1,936.89	285.36	2,222.25
65-69	216.27	30.67	246.94
TOTALS	52,678.53	10,908.29	63,586.82

SMSA = Standard Metropolitan Statistical Area

Results

In Tables 2 and 3 are summarized the observed and expected incidences of all cancers among the LLNL work force between 1969 and 1980. Among invasive cancers there appears to be an excess incidence of malignant melanoma of the skin and rectal and salivary gland cancers among women. Men had an excess of malignant melanoma of the skin and nervous system cancers other than brain and a deficit of lung cancers. No excess incidence of in situ cancers is evident.

Because the SEER Program does not include ascertainment of common skin cancers, namely basal and squa-

TABLE 2.—*Observed and Expected Number of Cancers Among San Francisco-Oakland SMSA-Resident Female Employees of Lawrence Livermore National Laboratory, 1969-1980*

Site	Number Observed	Number Expected	O/E Ratio
Invasive Cancers			
All sites combined	43	32.62	1.32
Lip (140)*	0	0.03	0
Tongue (141)	0	0.19	0
Salivary gland (142)	2	0.10	20.00†
Gum and other mouth (143,145)	0	0.16	0
Floor of mouth (144)	1	0.12	8.33
Oropharynx (146)	0	0.13	0
Nasopharynx (147)	0	0.07	0
Hypopharynx (148)	0	0.06	0
Pharynx, NOS (149)	0	0.01	0
Esophagus (150)	1	0.19	5.26
Stomach (151)	0	0.37	0
Small intestine (152)	0	0.05	0
Colon (153)	4	1.59	2.52
Rectum, anus (154)	4	0.76	5.26‡
Liver (155.0)	0	0.09	0
Gallbladder, other biliary tract (155.1,156)	1	0.13	7.69
Pancreas (157)	0	0.44	0
Retroperitoneum, peritoneum (158)	0	0.05	0
Other digestive organs (159)	0	0	0
Nasal cavity, sinuses, ear (160)	0	0.04	0
Larynx (161)	0	0.19	0
Lung and bronchus (162.2-162.9)	3	2.67	1.12
Mediastinum and other respiratory (162.0,163,164.2-164.9,165)	0	0.05	0
Bones and joints (170)	0	0.04	0
Soft tissue (incl. heart) (164.1,171)	0	0.20	0
Malignant melanoma of the skin (172)	7	1.35	5.19†
Other skin cancers (173)§	0	0.07	0
Breast (174)	8	11.02	0.73
Uterus, NOS (179)	0	0	0
Cervix uteri (180)	2	2.05	0.98
Corpus uteri (182)	4	3.85	1.04
Ovary (183.0)	4	1.70	2.35
Other female genital organs (181,183.2-183.9,184)	0	0.29	0
Urinary bladder (188)	0	0.33	0
Kidney and other urinary organs (189)	1	0.28	3.57
Eye (190)	0	0.04	0
Brain (191)	1	0.40	2.50
Other nervous system (192)	0	0.05	0
Thyroid gland (193)	0	1.20	0
Other endocrine (incl. thymus) (164.0,194)	0	0.05	0
Hodgkin's disease (201)	0	0.31	0
Non-Hodgkin's lymphomas (200,202)	0	0.66	0
Multiple myeloma (203)	0	0.14	0
Leukemias (204-208)	0	0.44	0
Primary unknown (199)	0	0.66	0

(Continued on next page)

(TABLE 2 *continued*)

Site	Number Observed	Number Expected	O/E Ratio
In Situ Cancers			
All sites combined	13	10.86	1.20
Buccal cavity and pharynx (140-149)	0	0	0
Stomach (151)	0	0	0
Colon (153)	0	0.07	0
Rectum, anus (154)	0	0.06	0
Larynx (161)	0	0.01	0
Lung and bronchus (162.2-162.9)	0	0	0
Malignant melanoma of the skin (172)	0	0.08	0
Breast (174)	0	0.81	0
Cervix uteri (180)	12	8.92	1.35
Corpus uteri (182)	1	0.54	1.85
Vagina, vulva (184)	0	0.32	0
Urinary bladder (188)	0	0.05	0

SMSA = Standard Metropolitan Statistical Area, NOS = not otherwise specified

*Number(s) in parentheses represent *International Classification of Diseases, 9th Edition* (ICD-9) code.

†Exceeds 99% confidence interval.

‡Exceeds 95% confidence interval.

§Excludes basal and squamous cell carcinoma.

mous cell carcinomas, we cannot determine by this method whether or not an excess of those tumors has occurred. Of rare skin tumors (excluding the melanomas), however, only two cases occurred during this interval, both in men. One of these was a dermatofibrosarcoma and the other a malignant histiocytoma.

Table 4 presents observed-versus-expected ratios for cancer incidence of sites grouped on the basis of radiosensitivity. Included in the highly radiosensitive-site group are bone, thyroid and blood (the leukemias, excluding chronic lymphocytic leukemia). The moderately radiosensitive-site group consists of the lung and female breast. All other sites are included in the nonradiosensitive group, except melanoma of the skin, which is excluded from the table. No excess incidence appears among those sites associated with ionizing radiation by these criteria.

Discussion

This analysis confirms, using a broader time period and cruder reference rates, our previous finding[1] that an excess of malignant melanoma of the skin exists among LLNL employees. Cancer of a few other sites also differs significantly from expectation. Possible reasons for those differences must be considered.

Because more than 100 site and sex comparisons have been made, one would expect that a small number of observed-to-expected ratios would appear to be significant by chance alone. For a P value of .05, one might expect approximately 5 out of 100 comparisons to be significant by chance alone and, for a P value of .01, one might expect one comparison to emerge as significant by chance. Further, one might also expect the direction of differences to be about equal. We find six comparisons to exceed the 95% confidence interval and four of those to also exceed the 99% confidence interval. All but one of these comparisons is in the direction of an excess rather than deficit, though it is impossible to estimate the relative magnitude of the deficit for those sites with an observed value of zero—such as Hodgkin's disease and multiple myeloma among men and thyroid cancer among women.

TABLE 3.—*Observed and Expected Number of Cancers Among San Francisco-Oakland SMSA-Resident Male Employees of Lawrence Livermore National Laboratory, 1969-1980*

Site	Number Observed	Number Expected	O/E Ratio
Invasive Cancers			
All sites combined	134	140.63	0.95
Lip (140)*	1	1.97	0.51
Tongue (141)	2	1.69	1.18
Salivary gland (142)	2	0.67	2.99
Gum and other mouth (143,145)	1	1.33	0.75
Floor of mouth (144)	0	1.39	0
Oropharynx (146)	0	1.33	0
Nasopharynx (147)	2	1.01	1.98
Hypopharynx (148)	1	0.84	1.19
Pharynx, NOS (149)	0	0.10	0
Esophagus (150)	1	2.18	0.46
Stomach (151)	2	4.87	0.41
Small intestine (152)	0	0.30	0
Colon (153)	11	10.59	1.04
Rectum, anus (154)	4	6.49	0.62
Liver (155.0)	1	1.54	0.65
Gallbladder, other biliary tract (155.1,156)	1	0.83	1.20
Pancreas (157)	5	4.28	1.17
Retroperitoneum, peritoneum (158)	0	0.29	0
Other digestive organs (159)	0	0.07	0
Nasal cavity, sinuses, ear (160)	1	0.50	2.00
Larynx (161)	1	4.71	0.21
Lung and bronchus (162.2-162.9)	18	33.22	0.54†
Mediastinum and other respiratory (162.0,163,164.2-164.9,165)	1	0.72	1.39
Bones and joints (170)	0	0.53	0
Soft tissue (incl. heart) (164.1,171)	1	1.37	0.73
Malignant melanoma of the skin (172)	21	6.46	3.25†
Other skin cancers (173)‡	2	0.38	5.26
Breast (175)	0	0.39	0
Prostate gland (185)	14	10.06	1.39
Testis (186)	7	3.12	2.24
Penis and other male genital organs (187)	0	0.38	0
Urinary bladder (188)	10	7.49	1.34
Kidney and other urinary organs (189)	3	4.82	0.62
Eye (190)	1	0.36	2.78
Brain (191)	1	3.51	0.28
Other nervous system (192)	3	0.23	13.04†
Thyroid gland (193)	3	2.53	1.19
Other endocrine (incl. thymus) (164.0,194)	1	0.24	4.17
Hodgkin's disease (201)	0	2.24	0
Non-Hodgkin's lymphomas (200,202)	6	5.56	1.08
Multiple myeloma (203)	0	1.69	0
Leukemias (204-208)	3	3.33	0.90
Primary unknown (199)	3	5.02	0.60
In Situ Cancers			
All sites combined	3	2.79	1.08
Buccal cavity and pharynx (140-149)	0	0	0
Stomach (151)	0	0.03	0
Colon (153)	1	0.62	1.61
Rectum, anus (154)	0	0.56	0
Larynx (161)	0	0.36	0
Lung and bronchus (162.2-162.9)	0	0.03	0
Malignant melanoma of the skin (172)	1	0.34	2.94
Urinary bladder (188)	1	0.85	1.18

SMSA = Standard Metropolitan Statistical Area, NOS = not otherwise specified

*Number(s) in parentheses represent *International Classification of Diseases, 9th Edition* (ICD-9) code.

†Exceeds 99% confidence interval.

‡Excludes basal and squamous cell carcinoma.

TABLE 4.—*Lawrence Livermore National Laboratory Study: Observed (Obs) Versus Expected (Exp) Cancer Incidence by Radiosensitive Site Groups, 1969-1980*

Site Group	Men			Women			Total		
	Obs Number	*Exp Number*	*O/E Ratio*	*Obs Number*	*Exp Number*	*O/E Ratio*	*Obs Number*	*Exp Number*	*O/E Ratio*
Highly radiosensitive—bone, thyroid and blood (ICD-9 codes 170, 193, 204.0, 204.2-208)	6	5.42	1.11	0	1.55	0	6	6.97	0.86
Moderately radiosensitive—lung and female breast (ICD-9 codes 162.2-162.9 and 174)	18	33.22	0.54*	11	13.69	0.80	29	46.91	0.62*
Nonradiosensitive—all other sites except MM (ICD-9 code 172)	89	95.53	0.93	25	16.03	1.56†	114	111.56	1.02*
All sites, excluding MM	113	134.17	0.84	36	31.27	1.15	149	165.44	0.91

ICD-9 = *International Classification of Diseases, 9th Edition;* MM = malignant melanoma of the skin.

*Exceeds the 99% confidence interval.
†Exceeds the 95% confidence interval.

Even if it were possible to observe one-half case for each of these three-deficit site/sex categories, none of the observed-to-expected ratios would exceed their 95% confidence intervals.

These comparisons have been made for all races in both the LLNL and comparison populations. Because the LLNL work force has a higher proportion of whites (about 93%) than the San Francisco-Oakland SMSA (about 83%), sites that are less common among nonwhite races will be slightly underrepresented in the expected numbers. Hence, the overall observed:expected ratio for malignant melanoma of the skin may be overestimated by this method by as much as 10%. Likewise, sites more common among nonwhites will be somewhat overrepresented in the expected numbers, so that the observed:expected ratios for lung and prostate among men and uterine cervix among women may be slightly underestimated. These variations would not, however, have a major impact on the direction or magnitude of differences.

The observed-expected differences for malignant melanoma of the skin we accept as real, based not only on the consistency and strength of these data, but on our earlier analysis as well.[1] The observed deficit in the expected incidence of lung cancer among LLNL male employees may be a function of the higher socioeconomic status of LLNL men compared with their population counterparts. Although we have no reliable evidence regarding the prevalence of smoking among LLNL employees, we do know that the male LLNL work force is a highly educated group. Among men it has been well established that smoking, the primary cause of lung cancer, is inversely related to education.

Among women, higher socioeconomic status is usually associated with increased rates of cancers of the uterine corpus and breast and decreased rates of cervical cancer. The distribution of these cancers among female LLNL employees suggests that they represent average socioeconomic status. Social class is therefore not a likely explanation for the excess incidence of rectal cancer among women.

One way to assess if an environmental factor is likely to be responsible for an excess incidence in one sex is to see if the excess also exists in the other gender sharing the same environment. The rectal cancer excess is not confirmed in men. The excess incidence of malignant lesions of the nervous system (excluding brain) observed among men is not shared by women. Two other sites, however, do share consistency between genders. These are malignant melanoma and cancers of the salivary glands—although the salivary gland excess is not significant among men.

The excess incidence of salivary gland cancer in this cohort is difficult to interpret due to the small number involved. It should be noted, however, that malignant tumors of the salivary glands (particularly the parotid gland) have been reported to be significantly elevated among exposed A-bomb survivors, with a relative risk of 10 compared with unexposed persons.[12,13] A similar excess has also been clinically noted for exposure to x-rays.[14] Finally, in a recent case-control study of Los Angeles residents, salivary gland tumors were found to be associated with both radiation treatment of the head and neck and certain dosages of dental x-rays.[15]

The data by radiosensitivity-site groupings are presented to explore the possibility of an excess that may be etiologically related to exposure to ionizing radiation. As considerable debate exists in the literature on the biologic effects of low-level radiation on different tissues, these groupings may not necessarily be agreed upon by other investigators. Other site groupings are certainly plausible. The highly radiosensitive-site group, however, represents a well-founded, if conservative, selection of sites. These data do not suggest the existence of any excess. However, this analysis does not take into account individual differences in measured exposure to radiation. Also, these data are for morbidity among concurrently employed members of the LLNL work force compared with their same sex/age counterparts in the general population. This does not preclude the possibility of increased cancer morbidity later in life or of differences in cancer mortality, although this analysis provides no evidence for or against such possibilities.

In summary, the overall cancer experience of active LLNL employees does not appear to differ greatly from that of the general population of the San Francisco-Oakland Bay Area. A small number of sites would be expected to appear to be in excess or deficit in this cohort by chance alone. This is likely to be the explanation for the observed excesses for rectal cancer in women and cancers of the nervous system in men. Small deficits may also exist by chance for Hodgkin's disease and multiple myeloma among men and thyroid tumors among women, though the differences are not quantifiable. The observed deficit of lung cancer among LLNL men is likely to be due to a low smoking prevalence in this highly

educated group. The excess incidence for malignant melanoma of the skin is also not likely to be due to chance. Malignant melanoma has been considered separately elsewhere.[1] Cancers of the salivary gland are extremely rare and not well studied. The excess incidence noted for this site in this cohort is based on such a small number (four cases) that these results are difficult to interpret.

Grouping cancer sites by radiosensitivity criteria suggests that no excess incidence is evident as a function of general radiation exposure, though a stringent test of this hypothesis would require a determination of individual radiation dosages and an assessment of cancer by dose category. Overall, the evidence from this analysis for all sites of cancer suggests that aside from malignant melanoma, no other major excesses are evident among current LLNL employees.

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Medical Progress

Pathogenesis of Impaired Glucose Tolerance and Type II Diabetes Mellitus—Current Status

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The insulin response to glucose taken orally is increased in patients with impaired glucose tolerance (IGT) but decreased in those with type II diabetes mellitus. The insulin response to meals, however, is normal in patients with type II diabetes, although the glucose concentrations are obviously elevated. The acute insulin response to intravenously administered glucose is absent in cases of both IGT and type II diabetes when the fasting plasma glucose level exceeds 115 mg per dl. On the other hand, the response to other intravenously given secretagogues is either normal or nearly so. The absent acute insulin response to intravenously administered glucose can be restored by α-adrenergic blockade, prostaglandin synthesis inhibition, dopaminergic blockade and euglycemia.

Insulin antagonism characterizes patients with both IGT and type II diabetes. Those with IGT and mild diabetes mellitus (untreated fasting plasma glucose concentrations < 180 mg per dl) have a receptor defect probably due to down regulation. Diabetic patients with more severe type II diabetes show a postreceptor defect. The relation (if any) between receptor and postreceptor defects is unclear.

(Davidson MB: Pathogenesis of impaired glucose tolerance and type II diabetes mellitus—Current status [Medical Progress]. West J Med 1985 Feb; 142:219-229)

Type II or ketosis-resistant diabetes mellitus and impaired glucose tolerance (IGT) are common and are responsible for a great deal of morbidity and mortality in adults. Current treatment is imperfect, reflecting our ignorance of the pathogenesis of these disorders. The lack of appropriate animal models has forced investigations to be carried out in human subjects and necessarily slowed our progress. However, since the advent of the radioimmunoassay for insulin about 25 years ago and the more recent introduction of new in vivo techniques for assessing insulin sensitivity, a great deal of information has emerged in this area. At first glance, the pathogenesis of IGT and diabetes mellitus would seem to be either impaired insulin secretion, impaired insulin action or possibly some combination of the two. In this review I will summarize the information regarding these possibilities, provide enough background material for understanding the data in this rapidly changing area and attempt to draw some tentative (albeit speculative) conclusions based on our current knowledge.

Insulin Secretion

Stimuli Given Orally

The results of the first report[1] comparing insulin responses of patients with ketosis-resistant diabetes mellitus and control subjects are shown in Figure 1. The first obvious conclusion is that insulin lack is not the cause of diabetes in these persons. There are two caveats to this conclusion, however. Many of these patients were obese and subsequent reports[2] have clearly shown that obesity per se is associated with hyperinsulinemia. Therefore, to assess insulin secretion in cases of IGT and diabetes mellitus, weight-matched controls are mandatory. Thus, one cannot conclude from the results shown in Figure 1 whether or not insulin secretion was normal as obese nondiabetic control subjects were not used. The second difference between the diabetic patients and control subjects in Figure 1 is their pattern of insulin responses. The peak concentration of insulin in the nondiabetic persons occurred at one hour while insulin levels peaked later in the diabetic

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patients. This delayed peak of insulin has been found in many, but not all, patients with ketosis-resistant diabetes and seems to be independent of obesity—that is, obese subjects with normal glucose tolerance do not show it and both lean and obese persons with IGT and type II diabetes mellitus may. Its significance in the pathogenesis of altered states of carbohydrate metabolism is unknown.

In hundreds of subsequent publications attempts have been made to determine if insulin secretion in cases of diabetes was increased, normal or decreased when controls of appropriate weight were used. The answer finally seems to be in and involves a strict definition of the groups under study. Patients with IGT according to the criteria of the National Diabetes Data Group—that is, fasting plasma glucose concentrations of less than 140 mg per dl and two-hour values between 140 and 199 mg per dl during a glucose tolerance test[3]—have increased insulin secretion and many of them show a delayed peak to glucose taken orally.[4-6] Patients with overt type II diabetes—that is, fasting plasma glucose concentrations greater than 140 mg per dl and two-hour values greater than 200 mg per dl during a glucose tolerance test—have impaired insulin secretion after glucose is readministered orally.[4-6] These conclusions are substantiated in three cohorts of patients—a group from California (Figure 2), Pima Indians (Figure 3) and a Scandinavian population (Figure 4.)

The total insulin responses in 145 nonobese persons[4] are summarized in Figure 2. Normal glucose tolerance (group N) in this study is defined by the very sensitive Fajans and Conn criteria—that is, one-hour plasma glucose concentrations of less than 185 mg per dl and two-hour plasma values of less than 140 mg per dl. Borderline tolerance (BT) defines a group in which one of these values was exceeded and chemical diabetes (CD) those persons in whom both values were exceeded. The final two groups had mild and moderate fasting hyperglycemia. The results are expressed as the area subtended by the values for plasma glucose and insulin during a three-hour glucose tolerance test. It is apparent that the total insulin response is increased in CD patients and decreased in those with fasting hyperglycemia of greater than 150 mg per dl. A normal total insulin response occurred in those with borderline tolerance and mild fasting hyperglycemia (glucose levels between 110 and 150 mg per dl).

Figure 3 relates the two-hour plasma glucose and insulin concentrations during oral glucose tolerance tests in 396 nonobese and obese (> 125% desirable weight) Pima Indians, none of whom were receiving sulfonylurea agents at the time of the test nor had ever received insulin.[5] The pattern is obvious. As the two-hour glucose value increases up to about 200 mg per dl, the insulin level is greater than normal. Further increases in the two-hour glucose value were associated with a

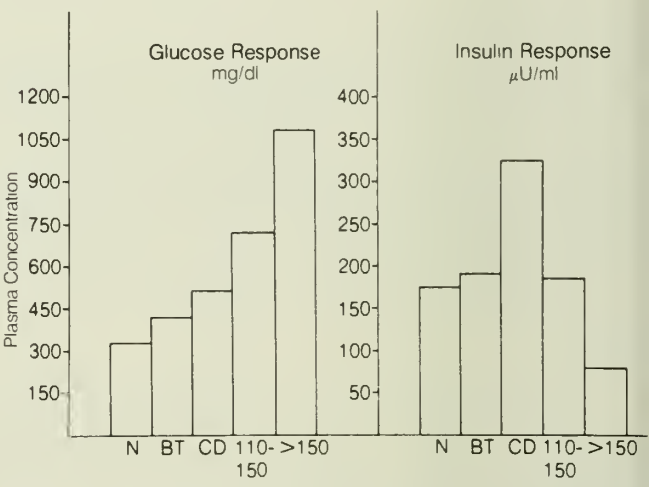

Figure 2.—Total glucose and insulin responses during oral glucose tolerance tests. See text for description of patient groups and method of expressing results. (From Reaven GM, Carbohydrate metabolism in insulin-independent diabetes, The Role of Sulfonylureas in the Treatment of Insulin-Independent Diabetes, published for Pfizer Laboratories Division, Pfizer Inc, by Science and Medicine Inc, 1980, pp 7-12. This figure summarizes data published in Reaven et al.[4])

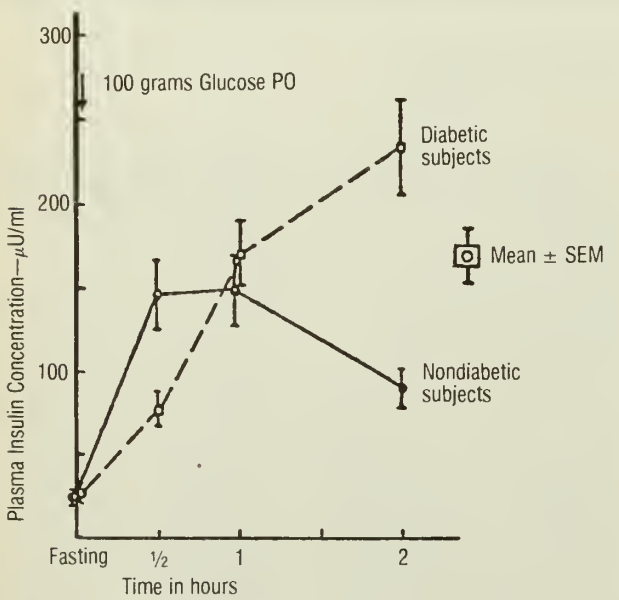

Figure 1.—Insulin response during an oral glucose tolerance test in 17 patients with "early maturity-onset" diabetes and 14 control subjects (from Yalow and Berson[1]). PO = by mouth, SEM = standard error of the mean.

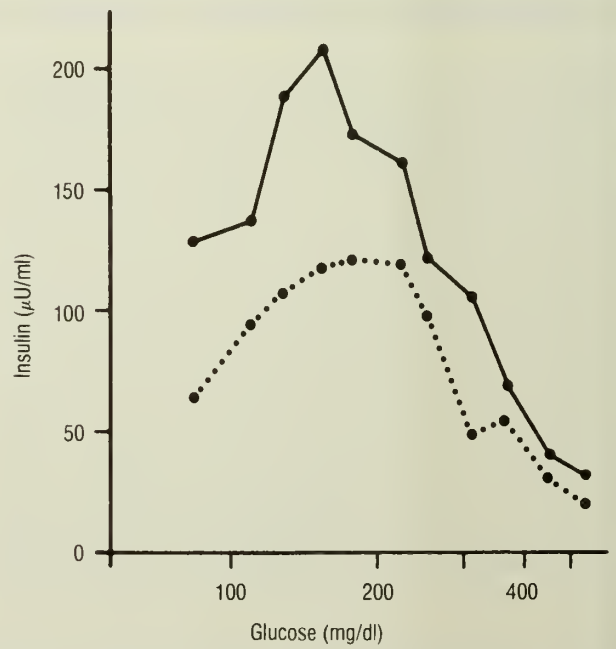

Figure 3.—Mean two-hour serum insulin and glucose concentrations in nonobese (●---●) and obese (●—●) Pima Indians (from Savage et al[5]).

declining insulin level, which soon fell to below normal. Note that although insulin concentrations are increased in obese subjects compared with lean ones as mentioned previously,[2] the same general pattern exists within each group.

The Scandinavian group[6] consisted of 165 control subjects and 85 persons with varying degrees of abnormalities on oral glucose tolerance testing. These latter patients were divided into five groups with progressive deterioration of glucose tolerance (bottom row of Figure 4) and each group was compared with sex- weight- and age-matched control subjects.

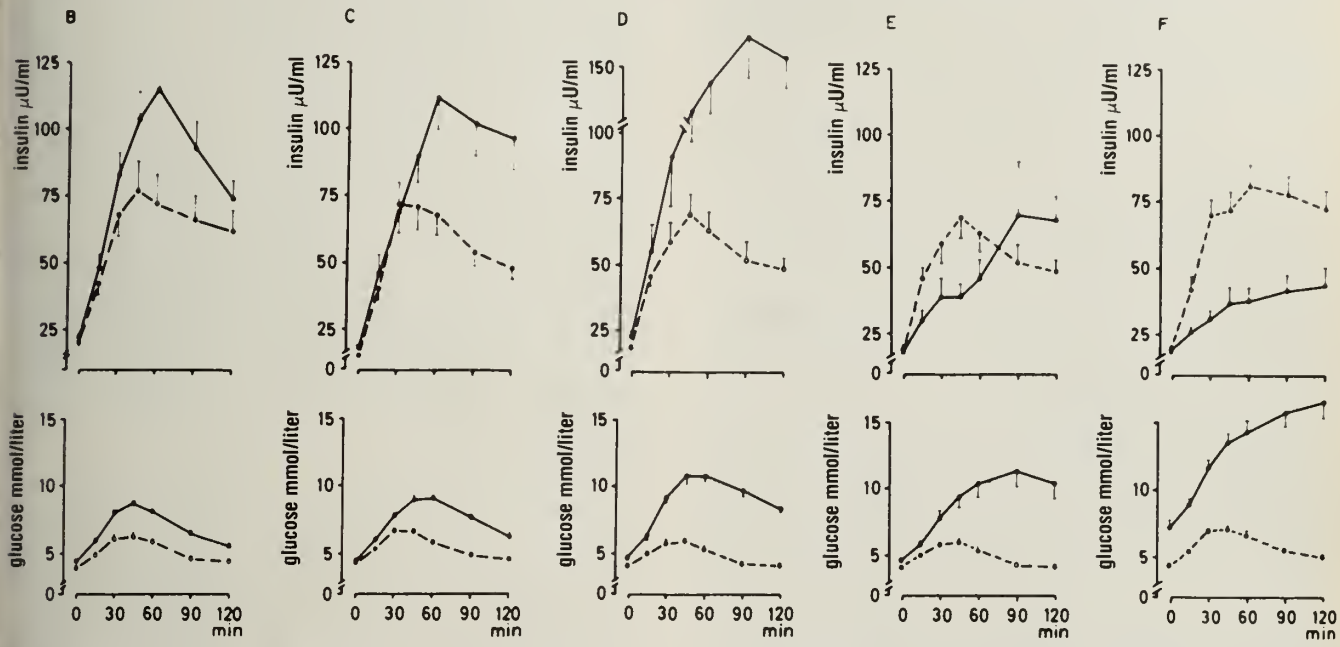

Figure 4.—Glucose and insulin responses during oral glucose tolerance tests in Scandinavian patients, with varying degrees of abnormalities depicted by the solid lines compared with sex-, weight- and age-matched controls depicted by the broken lines (from Luft et al[6]).

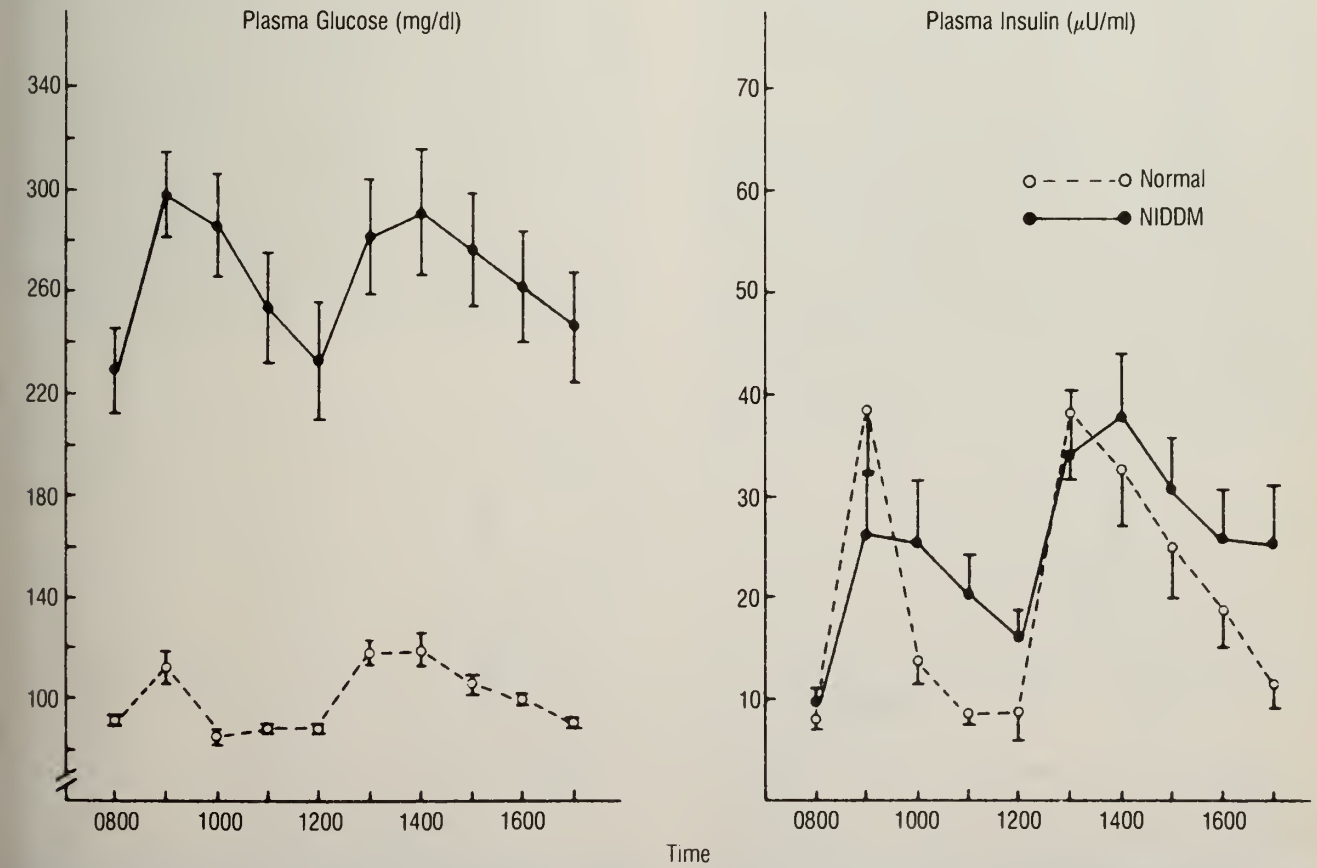

Figure 5.—Plasma glucose and insulin responses (mean ± standard error of the mean) to a mixed meal in 15 patients with type II diabetes and 15 controls. All subjects received breakfast at 0800 and lunch at 1200 (from Liu et al[8]). NIDDM = non-insulin-dependent diabetes mellitus.

The glucose units (mmol per liter) in the figure should be multiplied by 18 to convert them into milligrams per deciliter. The insulin responses are depicted in the top row of Figure 4 and are increased in the the first three groups of patients (B, C and D) with the mildest degrees of abnormality. In group E, the peak levels of insulin are normal, although attainment of the maximum concentration is delayed. Only in group F with the most severe deterioration of the oral glucose tolerance is the total insulin response clearly diminished.

Thus, a spectrum exists. Patients with impaired glucose tolerance (previously termed chemical or mild diabetes) have an enhanced insulin response to oral glucose. As the carbohydrate abnormality worsens, insulin concentrations return to normal and eventually diminish. Because in at least 20% of persons with IGT diabetes mellitus eventually develops,[7] it seems difficult to ascribe the development of clinically evident diabetes solely to a *primary* impairment of insulin secretion. For this to be true, one would have to subscribe to the view that IGT and diabetes mellitus were independent disorders, which does not seem likely.

Further evidence against a *sole primary* defect in insulin secretion as the basic cause of type II diabetes is the fact that the insulin response to meals in these patients is not decreased.[8] The results of two meal tolerance tests (which are obviously much more physiologic than 50 to 100 grams of dextrose) are shown in Figure 5. All sulfonylurea agent therapy in these lean type II diabetic patients was discontinued at least a month before these tests. Furthermore, they had the typical greatly impaired insulin response to glucose taken orally (data not shown) that characterizes these patients. The test meals were solid food of identical composition for breakfast and lunch, consisting of 40% carbohydrate, 40% fat and 20% protein. They provided 20% of the total daily caloric requirement for breakfast and 40% for lunch. The results are clear-cut. The insulin responses to the meals were similar in control and diabetic subjects. Two conclusions can be drawn from these "normal" insulin concentrations in the presence of this degree of hyperglycemia. First, the available insulin is not normally effective, a situation to be discussed below in detail. Second, because a nondiabetic person should be able to mount a much greater insulin response to this degree of hyperglycemia, the β-cell reserve of type II diabetic patients must be diminished. However, the fact remains that the tissues in these persons are exposed to the same levels of insulin throughout a 24-hour period as is the case in nondiabetic persons. Therefore, other factors must be involved in the pathogenesis of type II diabetes in addition to defects in insulin secretion.

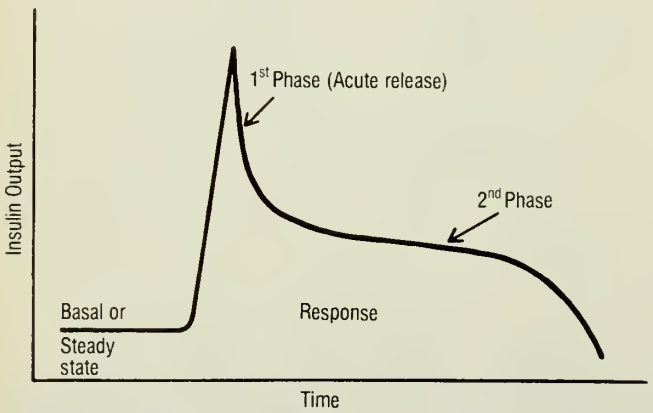

Figure 6.—Schematic representation of a normal insulin response to intravenous administration of glucose (from Pfeifer et al[9]).

Stimuli Administered Intravenously

Abnormalities in the insulin response to intravenous administration of glucose occur in patients with both IGT and type II diabetes mellitus, though how they may be related to the altered carbohydrate metabolism in these disorders is not yet clear. The normal insulin response to intravenously given glucose is shown in Figure 6. There is an initial rapid response with peak insulin concentrations reached within the first few minutes. This is called the first-phase or the "acute" insulin response. A more delayed gradual increase (termed the second-phase response) occurs if large amounts of glucose are administered or if the glucose is given continuously. A small pulse of glucose elicits only the first-phase response. Some other agents given intravenously will also stimulate a first-phase response. These include isoproterenol (Isuprel) hydrochloride, which is a β-adrenergic agonist,[10] glucagon,[11] tolbutamide,[12] certain amino acids such as arginine[13] and secretin.[14]

Persons with fasting glucose concentrations exceeding 115 mg per dl have an absent first-phase response to intravenously given glucose (Figure 7).[15] This obviously includes patients with both IGT and type II diabetes. However, the second-phase response to glucose given intravenously remains generally intact until the fasting plasma glucose level exceeds 200 mg per dl.[15]

In contrast to the absent first-phase response to intravenous administration of glucose, patients with both IGT and type II diabetes retain their acute insulin response to other intravenously given secretagogues such as isoproterenol,[10] arginine,[13] glucagon,[11] secretin[16] and tolbutamide.[17] Figure 8 depicts the acute responses to glucose and isoproterenol in normal persons and type II diabetic patients. Although the latter did respond to the β-adrenergic agonist, their mean response was somewhat less than that of normal subjects. More detailed analysis of the results in the diabetic population showed that the response to isoproterenol remained normal until the fasting plasma glucose concentration exceeded 300 mg per dl.[9]

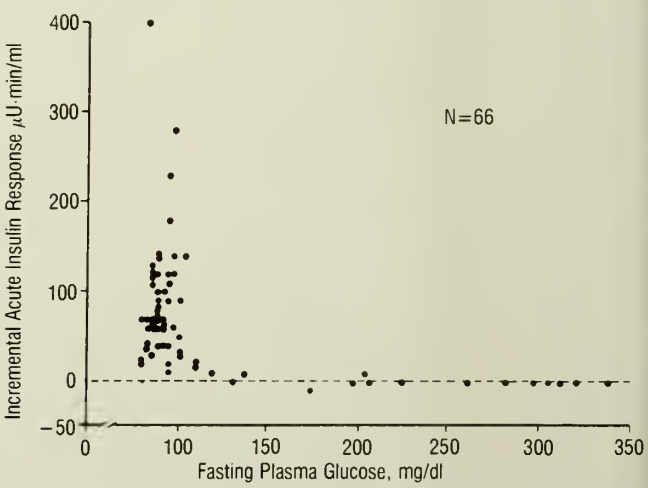

Figure 7.—Relation between fasting plasma glucose concentrations and the first-phase insulin response to intravenously given glucose (from Brunzell et al[15]).

Thus, the second-phase insulin response to intravenous administration of glucose became impaired with moderate decompensation, whereas impairment of the first-phase insulin response to isoproterenol only occurred with severe decompensation. These results suggest that the abnormalities of insulin secretion to intravenously given secretagogues may not be absolute. That is, they may vary depending on the degree of various metabolic or hormonal changes, or both. Indeed, it can be shown that the absent first-phase insulin response to glucose is not irreversible. It can be at least partially restored by the following manipulations: inhibition of prostaglandin synthesis[10]; α-adrenergic blockade[18,19]; opiate-receptor blockade,[20] and return to normal of the fasting glucose concentration by an overnight infusion of insulin.[17]

Because prostaglandin infusions, α-adrenergic agonists and dopaminergic stimulation will all inhibit insulin release in normal subjects, there is a molecular basis for the restoration of insulin secretion by the first three manipulations listed above. There is also a possible molecular basis for the effect of normalizing the fasting glucose concentration in restoring

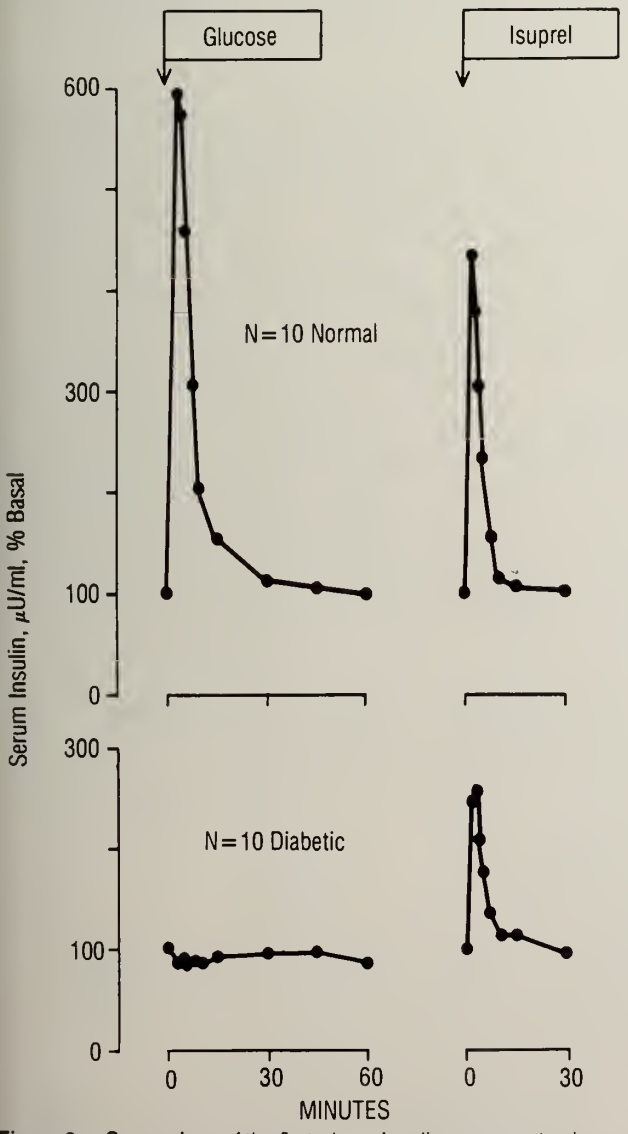

Figure 8.—Comparison of the first-phase insulin response to glucose and isoproterenol hydrochloride given intravenously in type II diabetic patients and controls (from Robertson and Porte[10]).

the acute insulin response to glucose given intravenously. If hyperglycemia is induced in *normal* subjects by a 46-hour infusion of somatostatin and glucagon, the acute insulin responses to glucose and isoproterenol mimic those found in patients with IGT and type II diabetes—an absent response to glucose and a normal response to the β-adrenergic agonist.[21] One interpretation of these results in normal subjects is that the alterations in insulin secretion to intravenous administration of secretagogues in patients with IGT and type II diabetes reflect a reaction to chronic hyperglycemia rather than a primary lesion of the pancreatic β-cell.

Insulin Antagonism

Insulin antagonism or resistance (these terms will be used interchangeably) occurs in any situation in which insulin is unable to exert its normal effect. Until 1970, insulin antagonism in human subjects was usually shown by either indirect means—such as normal or elevated glucose concentrations in the presence of elevated insulin levels following a glucose challenge—or by insulin tolerance tests. However, the latter test was not very sensitive as extremely high plasma insulin concentrations were attained. Furthermore, interpretation was hindered by the fact that different amounts of insulin were often given because of varying body weights. Finally, the contrainsulin (counterregulatory) hormones affect the results and this response is not related to insulin resistance per se.

Steady-State Plasma Glucose Technique

In 1970 Reaven and colleagues[22] reported a method that could show directly in human subjects more subtle degrees of insulin resistance. With this approach, termed the pancreatic suppression test, insulin suppression test or the steady-state plasma glucose technique, an infusion of insulin, glucose, propranolol hydrochloride and epinephrine is used. Insulin and glucose reach steady-state concentrations after 90 minutes and remain stable for at least an hour. The insulin level, termed the steady-state plasma insulin, is the same in all subjects, with the value depending on the rate of insulin infusion. The steady-state plasma glucose level is inversely related to the effectiveness of the infused insulin. Lower glucose concentrations reflect more effective insulin action whereas higher glucose values denote insensitivity to insulin. With this technique, Reaven and colleagues[2,22-30] found increasing insulin antagonism in lean subjects who have abnormalities in carbohydrate metabolism progressing from minor impairments of glucose tolerance through to overt diabetes mellitus (Figure 9). These results have been confirmed by other investigators in lean subjects with both impaired glucose tolerance[31] and overt diabetes.[32] However, because the unopposed α-adrenergic effect of propranolol and epinephrine can cause arrhythmias and hypertension,[33] this particular approach is now seldom used. More recently, somatostatin has been substituted for epinephrine and propranolol to block endogenous insulin secretion. Insulin resistance was again observed in lean and obese patients with both borderline glucose tolerance and overt diabetes.[34-37]

Euglycemic Glucose Clamp Technique

Recently, a more sophisticated method has been used to measure insulin sensitivity. With this approach, called the euglycemic clamp technique, a constant infusion of insulin (after an initial bolus) is given and variable rates of glucose

administered to maintain the glucose concentration at the basal value—that is, the glucose level is "clamped." This is accomplished by rapidly measuring glucose concentrations in blood specimens drawn every five minutes and adjusting the glucose infusion rate to maintain the desired concentration according to a predetermined algorithm.[38] The total amount of glucose administered is directly related to the effectiveness of the infused insulin; higher amounts of administered glucose reflect sensitivity to insulin whereas lower amounts indicate insulin resistance. Because the glucose concentrations remain constant, the rate at which glucose is disposed of is equal to the rate at which it is delivered into the circulation. This is the sum of the exogenous glucose administered by vein and the endogenous glucose produced by the liver. However, hepatic glucose production is suppressed by about 95% (even in diabetic persons) by these amounts of glucose and insulin and can

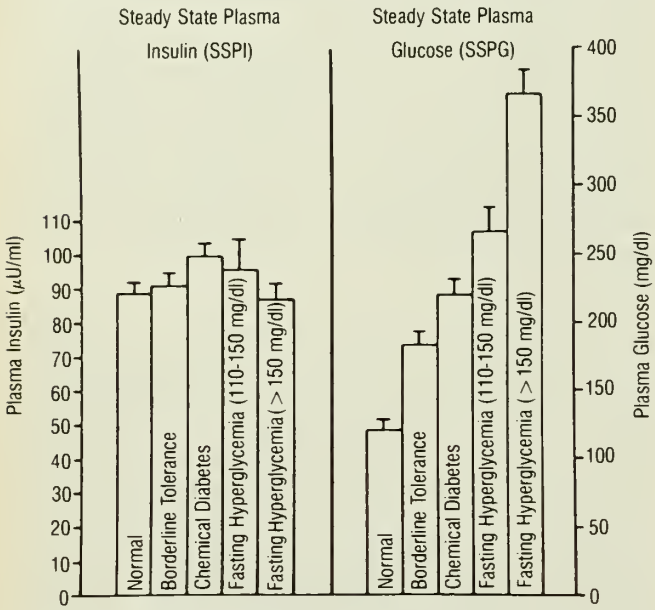

Figure 9.—Mean (± standard error of the mean) steady-state plasma insulin (SSPI) and glucose (SSPG) levels during the infusion of epinephrine (6 μg per minute), propranolol hydrochloride (0.08 mg per kg of body weight per minute), insulin (80 mU per minute) and glucose (6 mg per kg per minute) in five groups of patients. These patient groups are the same as those defined for Figure 2 (from Reaven et al[4]).

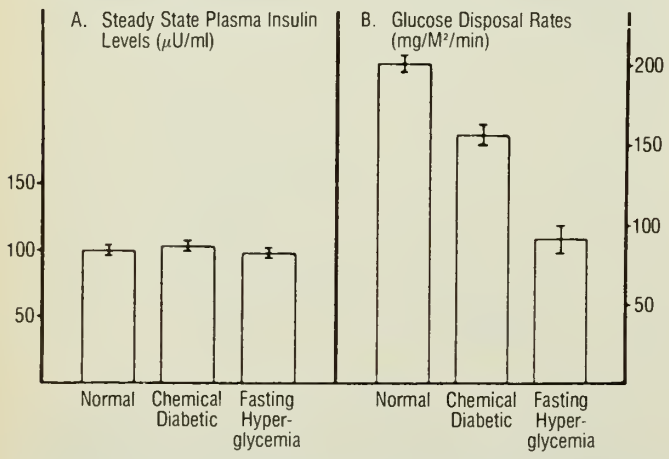

Figure 10.—Mean steady-state plasma insulin levels (A) and glucose disposal rates (B) in normal subjects, patients with impaired glucose tolerance (chemical diabetes) and type II diabetes (from Olefsky[40]).

therefore be ignored. If the renal threshold is exceeded, however, the amount of glucose lost in the urine must be taken into consideration. The results are often expressed as the glucose disposal rate and, in the absence of glucosuria, is simply equal to the rate of administration of exogenous glucose.

Increasing insulin antagonism has also been shown with the clamp technique as impaired glucose tolerance (chemical diabetes) worsens to overt diabetes (Figure 10).[30,39-45] Although obesity per se is associated with insulin resistance, once diabetes supervenes, the degree of insulin antagonism is similar in obese and nonobese persons with type II diabetes when measured by the clamp technique.[43]

Thus, a number of in vivo studies[2,22-37,39-45] have clearly established that insulin antagonism characterizes impaired glucose tolerance and type II diabetes mellitus. Unraveling the mechanism of this insulin resistance, however, has not been easy. Part of the reason involves the complicated set of circumstances governing insulin action and insulin antagonism. An understanding of these sophisticated concepts is necessary before assessing the current state of knowledge of the mechanism of insulin antagonism in patients with abnormal carbohydrate metabolism.

Insulin Binding

Binding of insulin to its receptor is the critical first step of insulin action. The interaction between hormones and receptors is influenced by two general properties: the number of available receptors (also termed the binding capacity) and the affinity or "attraction" between the hormone and its receptor. Hormonal binding affinities and capacities are usually quantitated by plotting the ratio of the bound hormone divided by the free hormone against the amount of hormone bound to the receptor at equilibrium.[46] Examples of this relationship (termed the Scatchard plot) for growth hormone and insulin are shown in Figure 11. Interpreting Scatchard plots is straightforward and calculations of the properties of hormonal binding are simple if a straight line relationship is obtained as in the case of growth hormone. The X intercept represents the total binding capacity and the slope of the curve defines the affinity. Evaluating curvilinear Scatchard plots, which characterize insulin binding, is more controversial. The two current leading interpretations are that the curve depicts either two classes of receptors[48] or a single class of receptors whose affinity for insulin diminishes as more and more insulin becomes bound.[47] However, binding capacities are still represented by the intersection with the X axis and the affinities by the slope of the curve. Because the validity of the

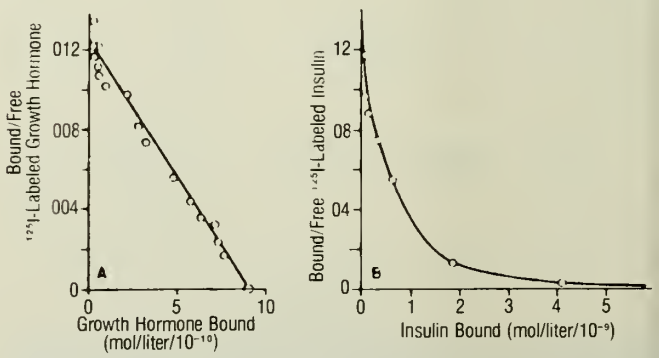

Figure 11.—Scatchard plots of growth hormone and insulin binding in cultured human lymphocytes (from de Meyts et al[47]).

Scatchard plot for insulin binding has been challenged,[49] the data concerning insulin binding (especially binding capacities) in type II diabetes (see below) should be interpreted cautiously.

There is an inverse relationship between circulating insulin concentrations and insulin binding. The "down regulation" of binding in the presence of increased levels of insulin[50] and "up regulation" when insulin concentrations are low[51] are an intrinsic characteristic of cells because lymphocytes in culture also show diminished insulin binding when exposed to high concentrations of insulin in vitro.[52] The reciprocal relationship between insulin concentrations and insulin binding is probably explained by the sequence of events that occurs after insulin binds to its receptor. The insulin-receptor complex is internalized into the cell where the hormone and, to some extent, the receptor are degraded in lysosomal structures.[53] Enhanced insulin binding in response to higher plasma insulin concentrations increases this process, which presumably leaves less available insulin receptors on the surface of the cell for subsequent binding.

Insulin-sensitive tissues contain spare or excess insulin receptors. Only 2% to 10% of the receptors on fat cells need to be occupied for insulin to exert its maximal effect[54]; for muscle, the proportion is 20%[55] and, for liver, 35%.[56] Thus, about 90% to 98%, 80% and 65% of the receptors on fat, muscle and liver, respectively, are spare or extra.

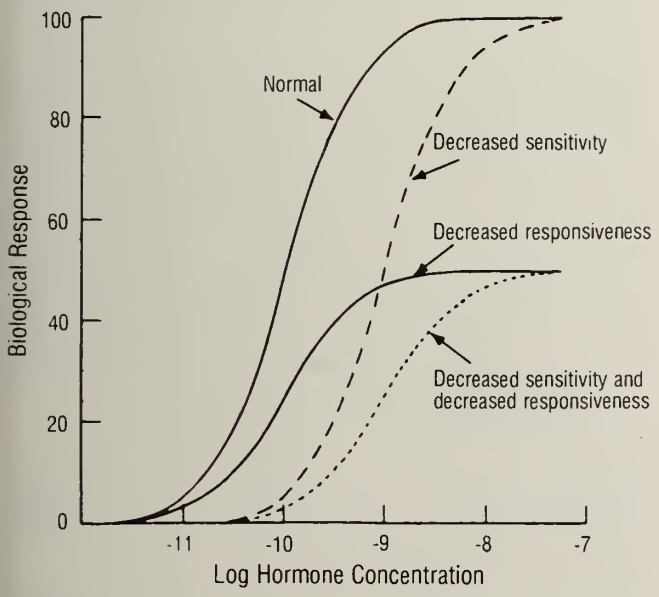

Figure 12.—Tissue sensitivity and responsiveness to hormonal stimulation (from Kahn[57]).

Tissue Sensitivity and Responsiveness

In a seminal paper in 1978, Kahn[57] discussed insulin resistance in terms of decreased sensitivity or responsiveness (or both). Characterization of insulin antagonism in these terms requires a full dose-response curve (Figure 12). If the curve is shifted to the right but the maximal effect is eventually attained, decreased sensitivity is present. That is, at submaximal concentrations of insulin, the effect is blunted, but at maximal levels a normal response is seen. Dose-response curves can be compared easily in terms of sensitivity by ascertaining the concentrations of insulin that cause 50% of the maximal effect. A higher value denotes insensitivity compared with the appropriate control situation. If a normal maximal effect is not attained regardless of how high an insulin concentration is used, decreased responsiveness is present (Figure 12). Decreased sensitivity and decreased responsiveness can occur separately or together (Figure 12).

Evaluating insulin antagonism in terms of decreased sensitivity or decreased resistance or both helps to delineate the mechanism(s) involved. A receptor defect (decreased insulin binding capacity) was postulated to cause diminished sensitivity whereas a postreceptor defect caused impaired responsiveness.[40] The reasoning is as follows. The interaction between a hormone and its receptor can be viewed as a random event. As the number of receptors decreases, it is less likely that an insulin molecule will find and interact with its receptor at a given hormone concentration. Therefore, an increased concentration of insulin is necessary in this situation to ensure that on a random basis the same number of receptors is occupied as in the normal state. This is consistent with the observations defining decreased sensitivity—that is, to obtain commensurate effects of insulin at submaximal levels, higher concentrations are needed until a maximal effect is reached (Figure 12).

To understand the mechanism underlying decreased responsiveness, a series of chemical reactions of a metabolic pathway within a cell may be represented as A → B → C → D → E. If the rate-determining step in this sequence is the C → D reaction, no matter how much or how fast substrate A is converted to compound C, the appearance of E will depend on the rate of C → D. To translate this into the series of events that occurs when insulin acts on peripheral tissues, the A → B reaction represents insulin binding to its receptor; B → C, the transport of glucose into the cell, and C → D, a number of intracellular reactions that eventually lead to the final reaction, D → E. This reaction culminates in the appearance of substance E whose production is increased by insulin (Figure 13). Therefore, if one of the rate-determining intracellular

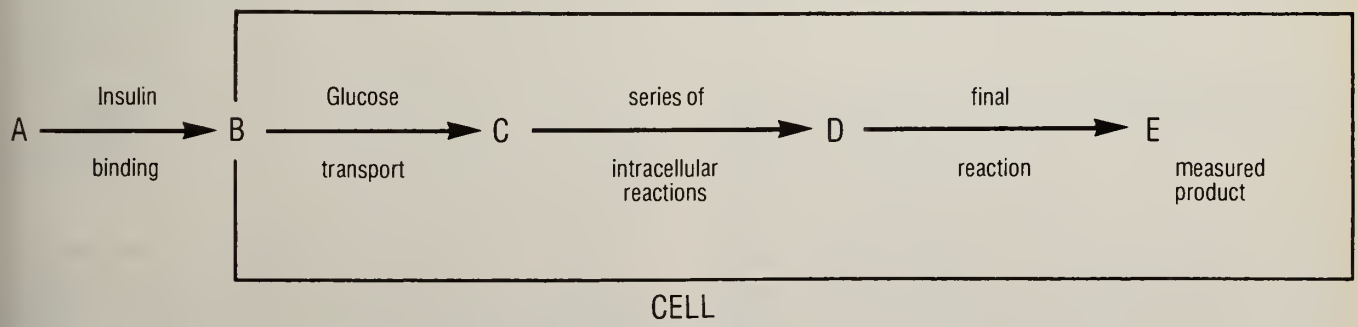

Figure 13.—Representation of insulin-stimulated intracellular metabolic pathway.

TABLE 1—*Relationship Among Insulin Binding, Sensitivity and Responsiveness in Various Clinical and Experimental Situations*

	Insulin Binding	Dose-Response Curves* Sensitivity	Responsiveness	Defect	References
A	Decreased	Right-shifted	Normal	Receptor	41, 42, 59
B	Normal	Normal	Decreased	Postreceptor	60, 61
C	Decreased	Right-shifted	Decreased	Receptor and postreceptor	59, 62-64
D	Normal	Right-shifted	Decreased	Postreceptor	65-67
E	Normal	Right-shifted	Normal	Postreceptor	68-71

*Insulin action versus extracellular insulin concentration.

reactions (C → D) is inhibited, no matter what concentration of insulin to which the tissue is exposed or what changes occur in the initial step of insulin binding, the maximal response to insulin (measured as the production of E) cannot be raised to normal. Thus, decreased responsiveness to insulin is thought to be due to alterations in the reactions within the cell and is therefore labeled a postreceptor defect.

Decreased responsiveness could theoretically also be caused by a diminished binding capacity if the number of receptors fell below the percent that had to be occupied to give a maximal response. Because of the presence of spare or excess receptors, this would mean a decrease to less than about 90% of normal in fat,[54] 80% in muscle[55] and 65% in liver.[56] With the exception of a few rare situations[58] not involving cases of type II diabetes mellitus, decrements in insulin binding capacities have been less than 50%. Therefore, a postreceptor defect remains a valid explanation for decreased responsiveness.

Since the initial formulations concerning the relationships among sensitivity and responsiveness and receptor and postreceptor defects were reported,[40] a number of other combinations have been described (Table 1). The first three situations in Table 1 were the ones discussed above. The remaining two situations in Table 1 (D and E) show that postreceptor defects can also cause decreased sensitivity and the last situation shows that a postreceptor defect may cause *only* decreased sensitivity—that is, responsiveness is normal. Reviewing all of the reported combinations in Table 1 suggests that the following simpler approach to assigning receptor or postreceptor defects (or both) to states of insulin resistance may be valid. If decreased binding is present, there is a receptor defect. If binding is normal, a postreceptor defect must be the cause of the insulin antagonism. In the presence of a receptor defect (decreased binding), a postreceptor defect is also present if decreased responsiveness (impaired maximal response) can be shown. With this formulation, it would be unnecessary to determine whether the dose-response curves were shifted to the right to delineate the site of insulin antagonism.

Application to Patients With Impaired Glucose Tolerance and Type II Diabetes

With these fundamental concepts regarding insulin binding and action in mind, let us turn to the situation in patients with abnormal carbohydrate metabolism. Some of the earlier studies did not differentiate between overt and chemical diabetes (now termed impaired glucose tolerance) but wherever possible they have been separated here. Insulin binding to monocytes[26] and adipocytes[41,72] removed from lean subjects with impaired glucose tolerance was decreased

TABLE 2—*Relationship Among Fasting Insulin Concentration, Insulin Binding and Insulin Action*

	Insulin Concentration	Binding	Action	References
A	Increased	Decreased	Decreased	26, 41
B	Normal	Decreased	Decreased	39, 42
C	Normal	Normal	Decreased	26, 32, 35,* 81, 84

*Fasting insulin levels were elevated.

and Scatchard plot analysis in all three reports showed diminished binding capacities. Insulin binding was normal, however, in obese patients with impaired glucose tolerance.[35] Insulin binding (only tracer binding was measured) was also decreased in monocytes from lean subjects with normal results on oral glucose tolerance testing but with a family history of diabetes.[73] Diminished insulin binding was also noted in cases of overt type II diabetes. Specifically, it was decreased in monocytes,[26,39,42,74,75] erythrocytes[76-78] and adipocytes[41] from lean patients and monocytes,[73] erythrocytes,[79] adipocytes[41] and T lymphocytes activated in vitro[80] from obese diabetic persons. Normal insulin binding, however, has been noted in some studies.[26,32,45,81-86] One wonders whether normal insulin binding in patients with altered carbohydrate metabolism may be more common but unreported in view of the number of published papers in which decreased binding has been observed. Scatchard plot analysis showed a diminished binding capacity and no change in binding affinities in all cases in which binding was decreased.[39,41,42,74,77,78,80] In one study in which tracer binding was normal, a decreased capacity was offset by an increased affinity.[83]

Insulin concentrations were measured in many of these studies. After oral glucose was administered, they were elevated in patients with impaired glucose tolerance[26,85] and decreased in those with overt diabetes.[26,32,82,83] Fasting levels were either normal[26,32,39,78,81-84,87] or elevated.[26,35,41,74-77,80,87] Because impaired insulin action was also found in some of these same studies,* it is instructive to examine the relationship among insulin concentrations, binding and action (Table 2). No consistent pattern is apparent. In situation A of Table 2, decreased insulin binding could contribute to the insulin antagonism possibly through the mechanism of down regulation. Diminished insulin binding could also be involved in the insulin resistance depicted in situation B, but it is not due to down regulation. However, situation C shows that the insulin antagonism associated with abnormal carbohydrate metabolism can occur in the presence of normal insulin binding.

Several other observations suggest that decreased insulin binding may not contribute fundamentally to the insulin resistance of these patients. Cultured skin fibroblasts from patients

*References 26, 32, 35, 39, 41, 42, 81, 84.

with overt type II diabetes[88] or maturity-onset diabetes of youth[89] bind insulin normally. In two studies (in which insulin action was not assessed),[87,90] the patients were divided into three groups depending on their insulin response to an oral glucose tolerance test. Insulin binding was increased in the low insulin responders, normal in the patients with a normal response and decreased in those with an enhanced response. Similarly, in a study in which insulin action was measured,[26] patients with considerable insulin resistance and normal fasting insulin levels had normal insulin binding, whereas other patients had less severe insulin antagonism, elevated fasting insulin concentrations and depressed insulin binding. These observations suggest that although changes in insulin binding may reflect local environmental factors—that is, insulin concentration—they do not constitute a primary abnormality in type II diabetes.

It is possible to construct dose-response curves in vivo using the clamp technique by infusing insulin at increasing rates to achieve circulating concentrations between 100 and 10,000 μU per ml on either different days or sequentially on the same day. The amount of glucose necessary to maintain the basal glucose concentration will increase in proportion to the insulin infusion rate and, when plotted against the plasma insulin level achieved at equilibrium, a typical sigmoidal dose-response curve is generated. Two groups have used this in vivo approach in patients with abnormal carbohydrate metabolism. Kolterman and co-workers[41] separated their patients into two groups of IGT and overt diabetes and found normal responsiveness in the former and decreased responsiveness in the latter (Figure 14). Rizza and associates[42] studied a single group of ten patients evenly split between having IGT and overt diabetes and they found normal responsiveness (Figure 15). Both studies showed decreased insulin binding and sensitivity in all groups of patients. Therefore, Kolterman and colleagues[41] concluded that a receptor defect characterized impaired glucose tolerance and both a receptor and a postreceptor defect were associated with overt diabetes. Rizza and co-workers[42] concluded that only a receptor defect caused the insulin antagonism of type II diabetes. Because the mean fasting plasma glucose concentration of Kolterman's patients with type II diabetes was 255 mg per dl, whereas the ten patients studied by Rizza and associates had an average fasting glucose level of 182 mg per dl, the resolution of these apparently discrepant conclusions may be that a receptor defect causes the insulin antagonism in patients with impaired glucose tolerance and mild type II diabetes and a postreceptor defect is responsible in patients with more severe decompensation.

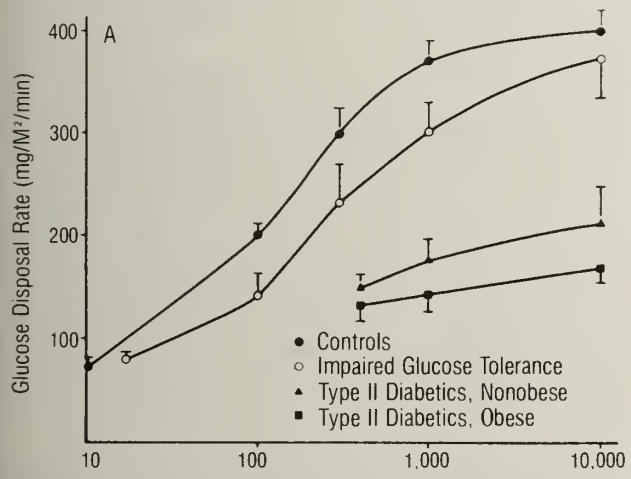

Figure 14.—Mean (± standard error of the mean) in vivo dose-response curves using the clamp technique (from Kolterman et al[41]).

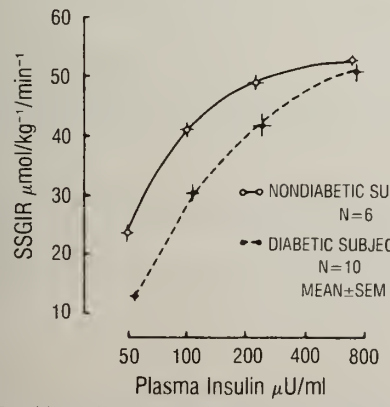

Figure 15.—Mean (± standard error of the mean) in vivo dose-response curves using the clamp technique (from Rizza et al[42]). SSGIR = steady-state glucose infusion rate

In vitro measurement of insulin binding and action in adipose tissue removed from patients with type II diabetes has also been used to evaluate the mechanism of insulin antagonism. This approach has failed to yield clear-cut answers as well. First, insulin binding has been reported to be both decreased[41] and normal.[84-86] Second, although the basal level of glucose transport in these adipocytes was depressed, the percent increase due to insulin has been normal.[86,90-92] Kahn[57] has pointed out the difficulty of evaluating the effect of insulin in the presence of differing baselines. A third difficulty is that antilipolysis responded normally to insulin whereas glucose utilization did not.[84,85] This discrepancy in the response of separate insulin-mediated pathways points toward a postreceptor defect.

Thus, the available information certainly indicates that insulin antagonism characterizes impaired glucose tolerance and type II diabetes. An important point to be considered is whether this insulin resistance is secondary to the altered carbohydrate metabolism or whether it constitutes a primary abnormality in these patients.

In several recent studies insulin binding and insulin action in patients with type II diabetes have been examined after one to eight weeks of intensive treatment with insulin. Greatly improved diabetic control was obtained with fasting glucose concentrations ranging from 70 to 140 mg per dl. The results have been mixed. The impaired insulin action before treatment was either mostly unchanged[32,93,94] or improved substantially but did not return to normal.[95-99] Insulin binding was either unchanged[32,95,98] or increased.[79,100] However, there was no correlation between changes in insulin binding and in vivo insulin action,[32,95,98] casting further doubt on the primacy of decreased insulin binding in causing insulin antagonism in type II diabetes.

Summary and Conclusions

The insulin response to glucose taken by mouth is increased in patients with IGT but decreased in those with type II diabetes. However, the insulin response to meals is normal in patients with type II diabetes, though the glucose concentrations are obviously much higher. The acute insulin re-

sponse to intravenously given glucose is absent in cases of both IGT and type II diabetes as long as the fasting plasma glucose concentration exceeds 115 mg per dl. On the other hand, the response to other intravenously given secretagogues, such as arginine, isoproterenol, tolbutamide, glucagon and secretin, is either normal or nearly so. The absent acute insulin response to intravenous administration of glucose can be restored by α-adrenergic blockade, prostaglandin synthesis inhibition, dopaminergic blockade and euglycemia.

Insulin antagonism characterizes patients with both IGT and type II diabetes. Because decreased sensitivity (a shift of the dose-response curve to the right) can be associated with both receptor or postreceptor defects, it does not seem necessary to measure full dose-response curves to differentiate between the two. Rather, decreased insulin binding defines a receptor defect and decreased responsiveness (impaired maximal insulin action) signifies a postreceptor defect. In general, a receptor defect (possibly related to down regulation of the insulin receptor) is associated with IGT and a postreceptor defect with type II diabetes. The relation (if any) between the two is unclear.

The following (tentative) conclusions seem warranted from the information currently available. For unknown reasons, in persons destined to have IGT and type II diabetes, insulin antagonism develops. Those whose pancreatic β-cells can meet this challenge by secreting increased amounts of insulin continue to have normal glucose concentration or IGT at the expense of hyperinsulinemia. Only in those with a genetic predisposition will type II diabetes develop. This predisposition involves a limited ability of the β-cells to continue to synthesize and secrete the extra insulin demanded of them. Thus, type II diabetes ensues when the β-cells can no longer respond well enough to prevent fasting hyperglycemia. This scenario is supported by a recent study[101] in which insulin secretion, insulin action and insulin binding in type II diabetic patients were evaluated by factor analysis and partial correlation analysis. The authors concluded that impairments of insulin secretion and action were of equal importance in causing the fasting hyperglycemia in type II diabetes, whereas decreased insulin binding was probably a secondary phenomenon.

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Specialty Conference

Computers in Medicine—The Office Setting

Discussant, MARC GELMAN, MD

This discussion was selected from the weekly Grand Rounds in the Department of Medicine, University of New Mexico School of Medicine.

RALPH C. WILLIAMS, Jr, MD:* In this conference Dr Marc Gelman, one of our residents most familiar with computers and their capabilities, will discuss an important subject—computers in medical practice. This topic should be of increasing interest to all of us.

MARC GELMAN, MD:†‡ Computers in the office setting deserve special attention because they represent an issue that affects many physicians who wish to purchase and use computers. It is of increasing importance, as evidenced by the numerous seminars attracting physicians and their money. Though I will be describing the merits of using computers in small group practices consisting of three to seven physicians, their wider applications will be self-evident. My purpose is to present what computers are capable of doing in an office setting today, portray future trends and concepts for computerization, including ethical and risk management considerations, and, last, offer thoughtful considerations and caveats toward the purchase of a computer. For purposes of orientation, a glossary of computer terminology is presented in Table 1.

Although a large number of articles addressing computers in medicine are cited in the *Index Medicus,* few references are listed that discuss their applications in the small group practice setting, presumably reflecting not only the infancy of computer use in clinical medicine but physician xenophobia as well. The information I have assembled, therefore, relies heavily on that supplied by computer vendors and personal observations.

I investigated what was commercially available from local vendors who sell software designed to operate on machines marketed by such manufacturers as Digital, International Business Machines (IBM), National Cash Register, Radio Shack and Texas Instruments. Common attributes of many of the systems are summarized in Table 2. Accessories to the basic system could provide such features as storage of brief narratives describing the patient-physician visit, custom designing of financial reports, variation of the billing cycle (determines when patients receive their bill), generation of bank deposit slips, collection letters for overdue payments, billing for hospital-based patients, lists of patients admitted to hospital and their bed assignments and appointment scheduling subdivided into five-minute blocks of time.

The microcomputer and minicomputer systems that I reviewed required only moderate training to achieve competence. The operating instructions were typically simplified by providing "menus" on the video screen that carefully detailed options to be selected at each step of the user-computer interaction. Systems cost between $8,000 and $150,000. The variation in cost was a function of the size of computer, memory, sophistication of software, number of terminals and after-sales support.

It was difficult to examine the differences between computerized and manual bookkeeping records in simple dollars and cents.[1] An example of one manual system is the pegboard, costing about $350 for a starter kit that is sufficient to maintain the needs of a single physician for one year. This system accommodates the activities of three to four physicians and generates a superbill. Insurance forms are avoided by requesting direct patient payment. The added value, however, of a computer limited to the group practice setting is realized in (1) decreasing the need for additional front office help as the practice grows; (2) simplifying and expediting billing to third-party payers; (3) helping to recognize procedures not economically viable; (4) improving the allocation of physicians' time; (5) aiding in preparing tax forms; (6) providing word processing, and (7) performing personal computing tasks. In addition, the actual cost of the computer is mitigated by the favorable tax treatment it receives in terms of investment tax credits and depreciation.

Though computers can improve front office efficiency, their role in electronic medical charting is much more provocative. Whereas a number of commercial systems is available, there is sparse literature describing meaningful experiences in the clinical environment. Two documented systems are described below.

The first system, situated in Hawaii, addressed front office functions and aspects of the back office.[2] The system, used in 1978 by a family practice group, provided an ongoing com-

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(Gelman M, Williams RC: Computers in medicine—The office setting—University of New Mexico School of Medicine [Specialty Conference]. West J Med 1985 Feb; 142:230-234)

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TABLE 1.—*Glossary of Computer Terminology*

back office Physical area staffed by physicians carrying out activities such as history taking and physical examinations that become part of the medical record

byte A byte (one character) is less than a word; 10 words = 1 line of programming

computer A machine that is capable of interpreting a sequence of instructions and delegating chores to such accessories as printers, video screens and memory devices

CPU Central processing unit: the brain in the computer. The speed with which the CPU can process information depends on a number of factors:

- the rate (defined in megahertz) of information stored in memory devices that can be called up;
- the size of words that can be read and processed at any one time: 8 bit-8 bit, 8 bit-16 bit, 16 bit-16 bit, 16 bit-32 bit, 32 bit-32 bit. Specifications of some popular microcomputers are as follows,

16-8 bit	8-16 bit	16-32 bit
APPLE IIC	IBM PC	APPLE Macintosh
1 MHz	4.7 MHz	8 MHz

- capabilities for virtual memory. The CPU anticipates information it requires from peripheral memory storage devices and shuttles data to itself to minimize wait time and make the internal memory appear to be of infinite size;
- the programming language used;
- the quality and elegance of software used.

cursor An electronic pointer that indicates to user and computer which information in the video screen is to be addressed

floppy disc A magnetic tape formulated on a disc, which is capable of storing from 140,000 to 1.2 million bytes of memory. The extent of storage depends on the diameter of the disc and the density (packing) of information

front office The physical area staffed by nonphysicians who perform activities that include billing, accounting, word processing and scheduling

hard disc A magnetic storage medium that stores and retrieves information much more quickly than floppy discs. This would be the preferred storage device to handle medical information at the present time. Floppy discs or magnetic tape would still be required to back up hard discs. Some hard discs even have exchangeable discs to more readily expand memory capabilities

internal memory Electronically stored information in semiconductor chips. This form of memory functions as a scratch pad to permit faster accession by the CPU. Storage of information for most 8- and 16-bit machines ranges from 32,000 to 512,000 bytes

language An interface between the computer and user that recognizes and executes instructions given the computer

laser disc An upcoming modality of mass storage that permits information to be optically and permanently stored onto a disc. This product is similar to the compact discs used to play stereo music. When compared with other forms of memory storage, its advantages are large, unerasable quantities of data—some ¼ million pages of data per disc

microcomputer The personal computer with 8 bit-16 bit technology, possessing limited speed and accession of internal memory. Its advantages are low cost and inexpensive and available software. Its primary disadvantages, relative to the minicomputer, are a lack of time-sharing to provide access to internal data bases, ability to handle simultaneous tasks and manipulate large amounts of data and access to sophisticated operating systems. Some of these distinctions are becoming blurred with advances in technology and decreasing costs

mouse A mechanical interface that is moved across a flat surface such as a desk to position a cursor on the video screen to rapidly retrieve information without the use of a typewriter keyboard

operating system A collection of instructions that enables the computer to handle housekeeping chores that supervise the processing of software and all output and input of information

software The instructions listed in a program (script) that are executed by the computer

superbill An itemized statement indicating previous amount owed, current procedures and services rendered and balance outstanding

user-friendly software Programs that interact with a user to provide self-documentation of instructions and commands and ease of operation

video display A television monitor that can display information from the computer

ABBREVIATIONS USED IN TEXT

IBM = International Business Machines, Inc.
MUMPS = Massachusetts General Hospital Utility MultiProgramming System
SOAP = Subjective, Objective, Assessment and Plan

puter record of a patient's visit summarized with two sentences describing each visit, a list of medications and a problem list limited to eight active problems. Furthermore, descriptions of each patient visit were handwritten in subjective-objective-assessment-plan (SOAP) format and were forwarded either as computer formatted or as is to the chart to be filed in shingle fashion (Figure 1). This system, maintaining both a traditional chart and the capability of retrieving electronically stored patient records (limited in scope), cost about $17,000—perhaps less today.

A more sophisticated system, MEDSTAR (a commercial version of COSTAR that uses an operating system called the

Patient encounter → Computer record of past encounters, problem list and medications → handwritten SOAP → word processing → chart

Figure 1.—Principles of the Hawaii system of computerization in a family practice group. SOAP = Subjective, Objective, Assessment and Plan.

Patient encounter → Computer generation of previous HPI, PE, PL, Labs, CXR and ECG and anticipated procedures → handwritten SOAP → Computer entry

Figure 2.—Principles of the Virginia system for a two-person office, using the Massachusetts General Hospital Utility MultiProgramming System. (See Table 3 for abbreviations used in figure.) SOAP = Subjective, Objective, Assessment and Plan.

TABLE 2.—*Attributes of Medical Office Computer Systems*

An itemized patient (super) bill, detailing prior and current charges for medical services, is generated for office-based procedures at the end of each month, billing cycle or office visit.

Automatic completion of insurance forms (some systems telephonically communicate with third-party payers for more rapid payment) is accomplished specifying patient, demographic information, diagnoses, services and procedures rendered, charges and credits.

Relevant information about account activities and balances can also be obtained—that is, it is possible to query accounts by individual, family, day, month or year and ascertain how one's accounts receivables are distributed in terms of outstanding debts versus settled accounts. Data can also be extracted from the computer to generate daily ledgers.

Data reflecting physician activity represent yet another computer capability. This information is relevant to physicians because it permits them to break down income-producing activities by specific services and procedures and judge their individual merits on an economic basis.

TABLE 3.—*Data Base Generated in Virginia System*

Financial status of patient
Problem list (PL)
History of present illness (HPI) and physical examination (PE)
Laboratory and other procedures deemed necessary on a preventative, maintenance basis—prompts user
Laboratory values (Labs)
Summaries of chest x-ray (CXR) findings
Summaries of electrocardiographic (ECG) results
Other tests

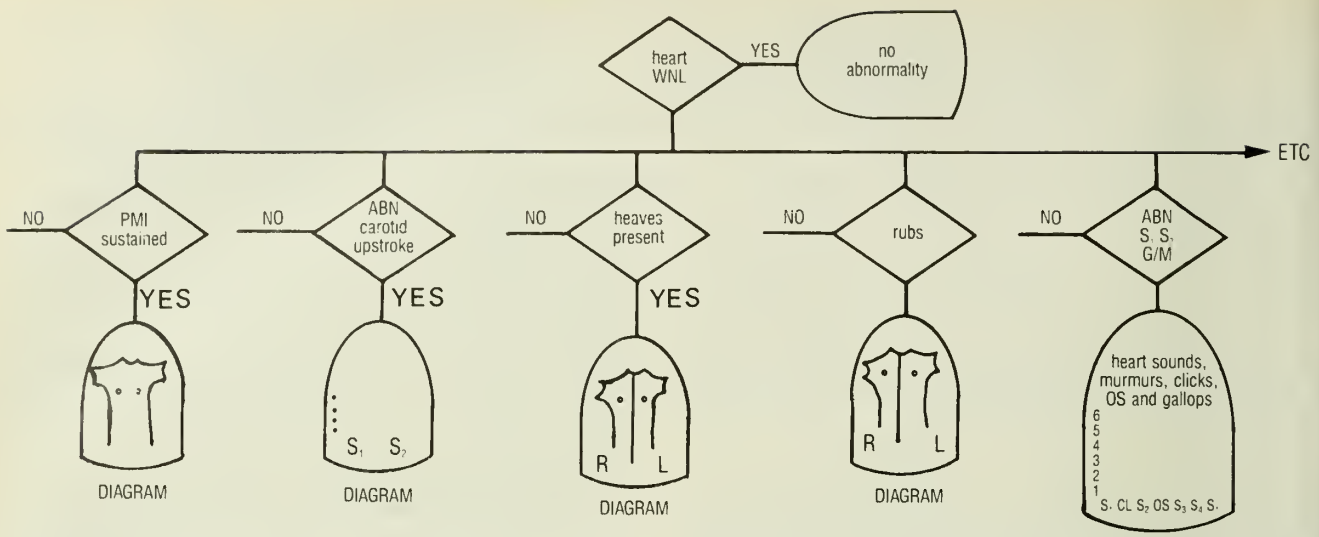

Figure 3.—A flow chart for a cardiac examination. WNL = within normal limits, PMI = point of maximal impulse, ABN = abnormal, G/M = gallop/murmurs, OS = opening snaps, R = right, L = left.

Massachusetts General Hospital Utility MultiProgramming System [MUMPS]), was used by a two-person practice in Virginia, one that came close to realizing a nearly paperless office. A summary of how these physicians interacted with their computer system to generate an integrated data base that describes an office visit is shown in Table 3. At a computer symposium in 1981, Hattick and associates reported that through a computerized chart review, they were able to better achieve health maintenance and to improve efficiency in seeing patients.[3] They stated that they were able to decrease by about 15% the time required to evaluate a case and record impressions in the SOAP format (Figure 2). Automated patient correspondence and generation of patient workups for prospective admissions to hospital were also realized. In 1982, an installed system cost between $18,000 and $30,000.[4]

Reasonable expectations for computers in the near future are indeed tantalizing. Some of these capabilities are discussed below.

Data Entry

Computers can function as repositories of patients' medical records. This has already been accomplished with such systems as MEDSTAR, which can store data representing patients' histories, physical examinations and laboratory reports. Comprehensive electronic medical charting, however, will be limited to only those advanced systems using *user-friendly* software. Apple's new LISA computer, specifically addressing middle-management business needs, nicely shows one company's concept of this term. LISA uses visual equivalents and a cursor directed by a mechanical device known as a mouse (see glossary in Table 1) to select and manipulate data. These capabilities provide an ease of operation necessary to gain physician acceptance of computers. Figure 3 shows how a physician using such concepts might, in the future, interact with a computer to pictorially describe a cardiac examination; the physician would indicate which portions of the examination were normal and which others were abnormal. Figure 4 shows a representation of an examination significant for a grade 2/6 systolic ejection murmur, a split second heart sound (S_2) and an S_3 and S_4 gallop.

Alternatively, in implementing data storage, speech may be used rather than keyboard entry. At the University of California at San Diego, members of the anesthesiology department have been developing a computerized transcription device that recognizes some 150 spoken words to generate a log (K. Davidson, "Operating Room Vocabulary—Doctors May Soon Talk to Computers," *Los Angeles Times*, Sep 15, 1983, p 18). In time, medical information could be directly communicated as speech to a computer. Though medical terminology seems better suited than other types for speech recognition because of the multisyllabled words often used, applications such as medical dictating are still at least a decade away from being implemented.[5]

Laboratory Records

Computers are capable of maintaining longitudinal records of laboratory values with the goals of recognizing trends and notifying health personnel of problems. Laboratory values could be pictorially displayed as a three-dimensional graph consisting of three axes representing specific laboratory values over time for all laboratories, respectively.[6] A lab-

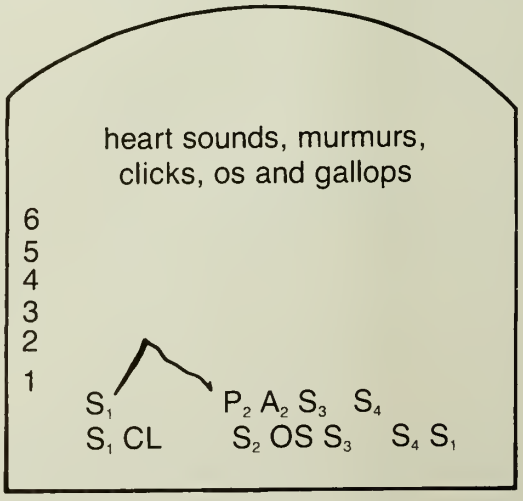

Figure 4.—A pictorial aid for a physical examination. OS = opening snaps, CL = click

oratory value could, for example, be defined as a weight, blood pressure or a potassium value.

Medication and Problem Lists

The ability to retrieve from electronic storage medication lists, problem lists and summaries of office visits enhances physicians' ability to care for their patients. These capabilities would facilitate rapid chart reviews, provide assessment of possible drug interactions, ease the preparation of prescriptions and aid in patient education and compliance by issuing relevant information about patients' diseases and their medications.

Consultations

Because computers are good at manipulating large amounts of information, they can offer consultation to a physician concerning a specific patient problem. Of necessity, these large data-based systems require the facilities of fast processing and large amounts of memory, presently limiting the microcomputer's accessibility to such tools (save the use of medical computer services and telecommunications). A group at Stanford University developed an artificial intelligence program to deal with issues of septicemia and meningitis. The program maintains an interactive dialogue with physicians from which a data base is constructed and the appropriate antibiotic regimen is selected, using Bayesian decision theory.[7] In contrast to many other artificial intelligence systems, this program's line of *reasoning* can be elicited to provide insight about how and why an antibiotic was selected. The computer system did as well as attending physicians in infectious diseases during an evaluation of ten challenging cases of meningitis, never failing to recommend the appropriate antibiotic coverage.

Another artificial intelligence program is the INTERNIST-I (CADUCEUS), which evaluated 19 Massachusetts General Hospital case presentations as reported in the 1969 issues of *The New England Journal of Medicine*. The program did well; it correctly identified 17 major diagnoses in contrast to 23 correct diagnoses by the primary physician and 29 by the discussants. The creators of this research tool (R. A. Miller, MD; H. E. Pople, Jr, PhD, and J. D. Myers, MD), however, recognized deficiencies that resulted in reliability problems when applied to the clinical setting. They noted that the program had limitations in the content of its knowledge base—that is, its ability to conceptualize temporally and anatomically and assume a broad overview of a problem, weighing (assigning importance) criteria that form algorithms, assigning causality and attributing specific data to simultaneous disease states.[8]

Continuing Medical Education

Large data bases contained in electronic and magnetic mediums, the increased prevalence of home computers that telephonically communicate and decreasing costs of telecommunications can greatly ease the way we learn and use information. Computers are capable of providing instructive patient management: physicians can be queried by a computer about how they would diagnose and treat patients with medical problems. Managing several cases per month over ten years would appear to provide more educational value through continuous study and would meet with less physician resistance than recertification examinations. The American Medical Association (AMA) and General Telephone and Electronics are developing the AMA/NET, a large data base that offers drug information, differential diagnoses premised on signs and symptoms and the beginnings of a literature base that will eventually be expanded to provide citations and abstracts.[9]

Diagnosis-Related Groups

Virtually all hospitals caring for Medicare patients since October 1, 1984, have been required to codify diagnoses into 467 categories to qualify for prospective payments to achieve cost-containment for the Medicare system (N. Macrae, "Health Care International," *The Economist,* 1984; 291:17-35).[10] Trends indicate that physicians' fees will also be subjected to such controls. If physicians are to substantiate claims made to government agencies and other third-party payers, quality assurance audits will be required. Unless records are computerized, this will be a nearly impossible task. Computers can provide the opportunity to define a new brand of medicine that will seek to balance the need to leave no stone unturned and the cost-health benefit to patients and communities.

Risk Management

Some 35% to 45% of all malpractice claims are rendered indefensible by problems with medical records.[11] Well-organized, legible and complete medical records are important to help convince a jury, if necessary, that a physician's assessment and plan mirror the concern for thoroughness suggested in a patient's chart. Computers can help provide quality records.

Computerized records pose other legal issues. Patients are entitled to request information contained in medical records.[12] Compliance with patients' requests, particularly if numerous in quantity, might well require an electronic means of information retrieval. Inherent in many written records are poor organization, problems of legibility and omissions that lead to errors in patient care. Perhaps rightly so, judges and juries will not tolerate errors based on acts of omission. Norris and Szabo, quoted in a *Journal of the American Medical Association* commentary, indicated that courts may come to expect that computers will be part of the legal standard of medical care.[13]

Confidentiality and Storage of Records

Whether information be present in Daniel Ellsworth's psychiatrist's files or contained on magnetic tape, it will remain accessible and vulnerable to misuse. A range of concepts and devices to protect the confidentiality of patients' records is available. Examples are restricting physical access to a computer, changing passwords frequently and using expensive ciphers that encode information into a near-infinite number of permutations.

Storing and retrieving information presents several problems. Times will arise when access to computer records will not be available because a computer is not functioning. Occasionally, magnetic tape and floppy-disc memory may be altered or lost, presenting authenticity problems and loss of patient records, respectively. Alternatives are microfiche, paper tape/cards and maintaining computer printouts initialed

by a physician. An intriguing alternative for the future is offered by laser discs, which optically record upwards of 275,000 pages of unerasable material onto 4.72- or 5.25-inch discs that are anticipated to be very cost competitive (K. Bergheim, L. McGeever, "Lasers Enhance Mass Storage," *Information World*, June 25, 1984; 3:40-45). Last, patients could wear a bracelet containing their entire medical record, which would be updated with each office visit and ensure availability of records.

Purchasing a Computer

I will now conclude with some practical considerations toward the purchase of computer systems. Advice summarized in Table 4 avoided mention of when, from whom and the size of computer system to purchase. These are the most difficult questions. Though it appears that IBM's personal computer has emerged as the industry standard for the microcomputer market, as evidenced by market share and look-alike copies, nothing of the sort can be said for its medical applications. The minicomputer market is even less clear in declaring a leader.

There is a general lack of a universal standard in hardware, let alone in a programming language. This lack of conformity results in diluted resources for developing software and in limited communication between physicians and their machines. The emergency room situation is an example where it might be critical to have access to information from a patient's private physician's computer to provide the proper care.

TABLE 4.—*Advice for Purchasing a Computer*

- Find a reliable dealer who specializes in medical software, offers prompt servicing of equipment and is likely to be staying in business.* A list of installations should be made available to customers. Service contracts on both the hardware and software will be required.
- Shop for software first, then buy your hardware. Software that is written for operating systems such as **UNIX** or **PICK** will provide important freedom—the ability to operate software on any brand of hardware that supports the operating system. Modifications to customize software are very expensive, costing from $35 to $50 per hour of programmer's time. It is important to shop comparatively for desired features. A system should allow for growth. Software needs to be simple to operate, particularly when using temporary office help. Also, consider the comfort of employees when purchasing such equipment. For example, the increased eye strain of some video monitors should be considered.
- Physician comments in the form of paragraphed text (such as a dictated discharge summary) are no substitute for an indexed, well-organized, electronic patient record-retrieval system. These criteria are prerequisites for searching and collating information that will permit data-base management.
- Buy the best quality peripheral devices available. Moving parts on printers and disc drives can break down and cause great aggravation.
- Inquire what provisions have been implemented to prevent employee embezzlement and limit access to confidential information. Audit capabilities will be very important towards achieving this end.
- Selection between a minicomputer and a microcomputer requires a proper definition of a physician-user's needs. Minicomputers, in contrast to microcomputers, offer more hardware features such as passwords, multiple task capabilities, simultaneous users and operating systems that permit more flexible filing of records and manipulating data bases. These distinctions, however, adding a great deal of cost, are becoming less obvious with the increasing technologic advances being implemented within the microcomputer industry.
- Performance guarantees in writing to ensure that the machine and software function as promised are important. Access to the source code in the event of software company default (bankruptcy) to permit easier software modifications is also worthwhile.

*From McCartney[14] and Zimmerman et al.[15]

TABLE 5.—*Computer Options for Practicing Physicians*

- Obtain a system at some cost to run both the front and back office.[4] As more systems of this sort become commercially available, comparison shopping can help physicians to better define their needs.
- Obtain a system that handles the front office and aspects of the back office, recognizing that vendor promises to provide future software advances are not always delivered.
- Defer buying until sufficient hardware and software maturation is achieved, perhaps in one to two years. The disadvantage of this option, however, is that there will be that much more in accumulated records that will need to be converted and entered into the computer.

Perhaps the federal government will provide the lead to encourage programming in MUMPS by its adoption at Veterans Administration Medical Centers across the country. MUMPS handles data in "dynamic (readily changeable), sparse and hierarchical files" well suited to handling medical billing and records.[16] An alternative is American Telephone and Telegraph's UNIX operating system, recently licensed to IBM, that permits portability of software between different brands of hardware that have adopted the *same* version of the UNIX operating system. A third choice, featuring not only portability but excellent data-base-management capabilities as well, is Dickpick's PICK system (R. Cook, "Operating Systems," *Popular Computing*, Aug 1984; 3:111-148). Confounded physicians are left with three options, and these are summarized in Table 5.

My appraisal of the present market is that, because of the costs and sophisticated programming required to implement comprehensive electronic medical charting, the capabilities of most commercial computer systems are limited to front office applications. I expect these obstacles to be better addressed with the decreasing costs of computers and memory and more simplified interfacing of the computer to users. A market that in the near future will exceed hundreds of millions of dollars should provide the commercial incentive to rectify these problems.

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Medical Staff Conference

Therapeutic Strategies in Congestive Heart Failure and the New Inotrope-Vasodilator Agents

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs Homer A. Boushey, Associate Professor of Medicine, and David G. Warnock, Associate Professor of Medicine, under the direction of Dr Lloyd H. Smith, Jr, Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

The use of the Foxglove is getting abroad, and it is better the world should derive some instruction, however imperfect, from my experience, than the lives of men should be hazarded by its unguarded exhibition, or that a medicine of so much efficacy should be condemned and rejected as dangerous and unmanageable.

WILLIAM WITHERING, 1785

DR SMITH:* *Each year it is our custom to ask the chief medical residents at the Moffitt Hospital (University of California, San Francisco) to give one of our Medical Staff Conferences. We are continuing that tradition with this conference. Dr Charles Simonton received his medical degree from Harvard. For the past four years he has served with distinction as a member of this house staff, especially in the leadership role implied in the chief residency. Next year he will return to his native North Carolina for fellowship training in cardiology at the Duke University Medical Center.*

DR SIMONTON:† The recent introduction of many new intravenous and oral positive inotropic agents for the treatment of congestive heart failure (CHF) places us at the threshold of the challenge faced by Withering two centuries ago. The foxglove often produced dramatic and life-saving effects in "cases lost to the common run of practice, and only snatched from destruction, by the efficacy of the Digitalis."[1] News quickly spread abroad that digitalis cured many cases of severe dropsy refractory to the treatments of the day, and Withering was pressed to report his cases and make recommendations concerning the use of digitalis.

Today, despite advances in our knowledge about the effects of digitalis as an inotropic agent in CHF, and despite potent diuretics and vasodilators, we continue to see patients for whom conventional therapies have failed and who desperately need increased inotropic support of the heart to maintain perfusion of vital organs. The widespread nature of heart failure in our society and the desperation of these patients have sparked major interest in two newly developed classes of inotropes—sympathomimetic and nonglycosidic, nonsympathomimetic agents. The purpose of this discussion is to examine these new inotropes, describe the background of our current understanding of the pathogenesis and treatment of the congestive heart failure syndrome and provide an update on current studies examining the immediate and long-term efficacy of these new agents in CHF.

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Pathophysiology of the Congestive Heart Failure Syndrome

The primary underlying defect for the clinical syndrome of CHF is a loss of contractile function and pump failure of the left ventricle, whether due to myocardial infarction, idiopathic cardiomyopathy, valvular disease or congenital anomalies. As the pumping function diminishes, several compensatory responses occur within the cardiovascular system to insure that blood pressure and adequate perfusion of vital organs are maintained. The first is an *intrinsic reflex increase in left ventricular end-diastolic volume*, maximizing the overlap of actin and myosin filaments within sarcomeres, which increases stroke volume and stroke work (the Frank-Starling mechanism, as shown in Figure 1). This reflex mechanism is limited, however, by the detrimental effects of increasing end-diastolic volume and pressure, producing increases in wall tension, myocardial oxygen consumption and pulmonary venous pressure leading to pulmonary congestion. In patients with poorly compliant left ventricles due to postinfarction fibrosis or myocardial hypertrophy, pulmonary venous hypertension may occur very early with the reflex increase in end-diastolic volume.

The second compensatory mechanism is an *increase in sympathetic nervous activity* in response to the reduction in cardiac output and fall in arterial pressure. Via adrenergic nerves in the heart and release of catecholamines from the adrenal medulla, myocardial contractility and heart rate are increased, resulting in improved stroke volume, stroke work and cardiac output. In addition, increased systemic venous and arterial tone leads to increased venous return (preload) and arterial resistance (afterload), respectively. The sympa-

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ABBREVIATIONS USED IN TEXT

ATPase = adenosine triphosphatase
CHF = congestive heart failure
NYHA = New York Heart Association

thetic stimulation of the heart represents a potent inotropic reflex available to a failing heart, and causes a shift of the end-systolic pressure-volume relationship toward a position of increased stroke volume at a relatively unchanged arterial pressure and end-diastolic volume (Figure 2). The adrenergic reflex in heart failure causes a chronic elevation of circulating norepinephrine that imposes high costs of myocardial oxygen consumption, increased impedance to left ventricular ejection and may even contribute to a selective reduction of myocardial catecholamine stores, cardiac sympathetic neuronal function and β-adrenergic receptors in these patients. Eventually the beneficial effect of catecholamines on contractility is outweighed by the detrimental effects of excessive oxygen consumption, arterial impedance and perhaps attenuated contractile response to catecholamine stimulation, resulting in further decline of left ventricular function.

Third, due to a reduction in arterial blood pressure and renal blood flow secondary to decreased cardiac output, renin-angiotensin-aldosterone secretion increases resulting in vasoconstriction and *salt and water retention.* Expansion of intravascular volume with most of the volume shifted to central venous and pulmonary compartments results in further maximizing the Frank-Starling mechanism by increasing preload, but at the expense of pulmonary and systemic venous hypertension and interstitial edema. The increase in systemic vascular resistance by angiotensin II impedes left ventricular ejection, which can be shown to be hemodynamically significant by the beneficial effects on left ventricular function of converting enzyme inhibition and by the reductions in plasma renin activity during compensation of heart failure.

Finally, the chronic volume and impedance loading of the left ventricle produces *myocardial cell hypertrophy*, a last attempt by the heart to compensate for reduced pumping function, which proves to be too little too late.

Hence, we are confronted with the hemodynamic features of greatly decreased cardiac output, low arterial pressure despite high systemic vascular resistance and pulmonary and systemic venous hypertension. Clinically, a patient suffers

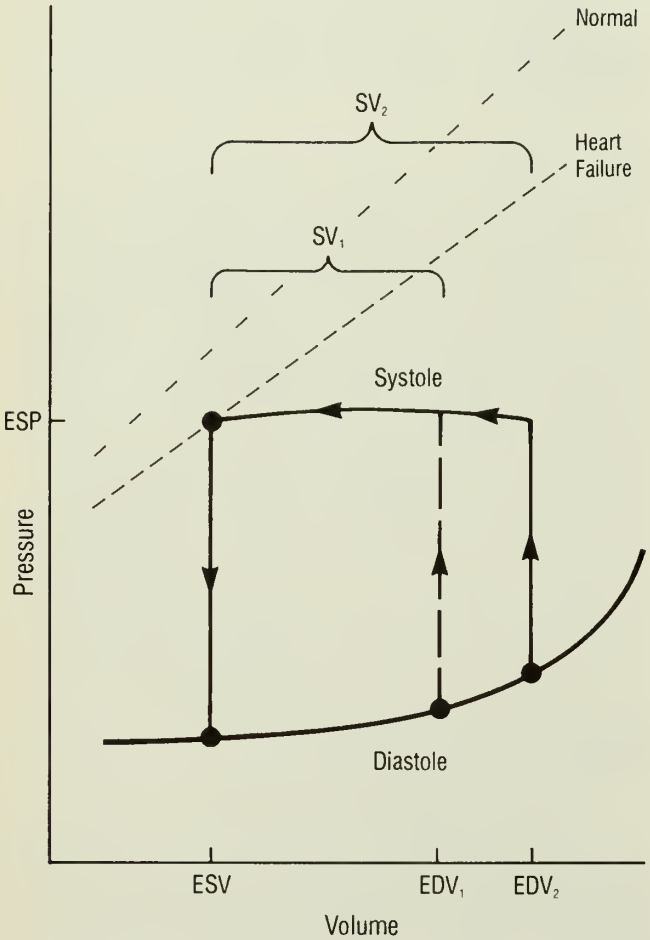

Figure 1.—The Frank-Starling mechanism in congestive heart failure. This schematic of the left ventricular pressure-volume relationship during the cardiac cycle in congestive heart failure shows the increase in end-diastolic volume (EDV) and stroke volume (SV) that occurs by the Frank-Starling mechanism. The dashed lines for normal and heart failure represent the end-systolic pressure-volume relations that define the contractile state. ESP = end-systolic pressure, ESV = end-systolic volume

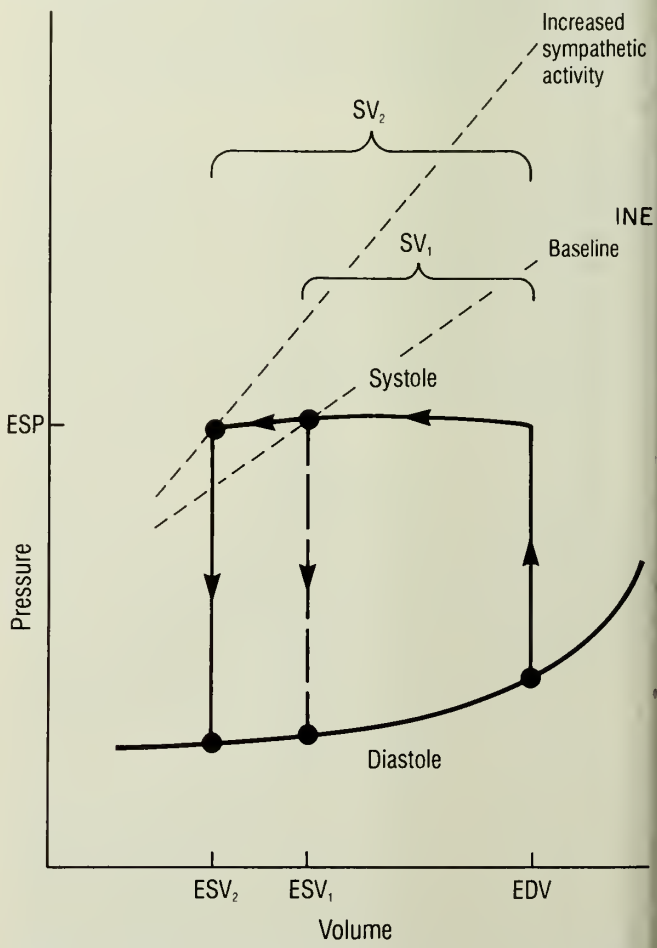

Figure 2.—Effect of increased sympathetic activity on ventricula function in congestive heart failure. This schematic of the left ventric ular pressure-volume relationship during the cardiac cycle shows the shift in the end-systolic pressure (ESP) and end-systolic volume (ESV relation and increase in stroke volume (SV) that occurs with increased sympathetic stimulation in heart failure. ESV_1, ESV_2, SV_1, SV_2 = end-systolic volume and stroke volume before and after reflex sympathetic stimulation, EDV = end-diastolic volume.

from fatigue due to reduced blood flow and redistribution of flow away from the musculoskeletal system to maintain vital organ perfusion; dyspnea due to pulmonary venous hypertension; edema due to systemic venous congestion, and life-threatening arrhythmias due to electrical instability of the heart in the setting of excessive catecholamine stimulation and imbalances in myocardial oxygen supply and demand.

Therapeutic Strategies

Given the overall hemodynamic characteristics of congestive heart failure, three major strategies have been developed for reversing the adverse consequences of a decline in ventricular pump function: *digitalis glycosides* to improve cardiac output directly by increasing contractility; *diuretics and salt restriction* to reduce the pulmonary and systemic venous congestion, and *vasodilators* to improve cardiac output by reducing systemic vascular resistance, arterial pressure and hence impedance to left ventricular ejection.

The digitalis glycosides represent the most time-tested, extensively studied and yet controversial class of agents in the treatment of heart failure. For two centuries, digitalis has served as the cornerstone of inotropic therapy in patients with heart failure. Yet debates concerning the cellular mechanism of its inotropic action and the efficacy of its use in clinical syndromes such as in acute myocardial infarction and chronic heart failure with sinus rhythm have continued into this decade.

Evidence for the direct inotropic action of digitalis on cardiac muscle was not established until 1938 by Cattell and Gold, who showed that digitalis increased the force of contraction in isolated cat papillary muscle. Progress was slowed for many years by the concept that digitalis had its inotropic effect only in the failing heart and not on normal myocardium, leading to the hypothesis that digitalis altered some biochemical event present only in heart failure. It has subsequently been shown many times that digitalis increases the force of contraction in normal as well as failing hearts.

The physiochemical basis for the positive inotropic action of digitalis, or of any pharmacologic agent that increases the contractile force of the heart, is best understood by examining the cascade of cellular events following the excitation of the myocardial cell membrane that culminate in the final interaction of actin-myosin contractile elements (Figure 3). Once the myocardial cell membrane is excited, either by neurotransmitters or other stimulants, the electrical phenomenon of rapid depolarization followed by slower repolarization—the action potential—takes place. The chemical basis for this event involves an initial rapid influx of sodium into the cell down its electrochemical gradient, followed by a slower but larger influx of sodium and finally, potassium efflux. During the slow influx of sodium—the plateau phase of the action potential—calcium influx also occurs, increasing the intracellular free calcium ion concentration. Part of the increase in intracellular calcium comes from stores on the inner surface of the sarcolemma, which then activate the release of a much larger pool of stored calcium from the sarcoplasmic reticulum. Free calcium ions then bind troponin C, altering the troponin-tropomyosin complex and releasing the inhibition on the myofibrillar contractile mechanism, resulting in contraction. The final common pathway for determining contractile force is dependent on the degree of elevation in free calcium ions at the site of the contractile elements. Hence, short of a direct effect on the contractile proteins themselves or an improvement in myocardial energy metabolism, any inotropic agent must have as its final effect an increase in intracellular free calcium ions.

Components of excitation-contraction coupling, which if altered might influence the availability of calcium to the contractile elements, fall into four major categories: (1) the configuration of the action potential influencing the inward

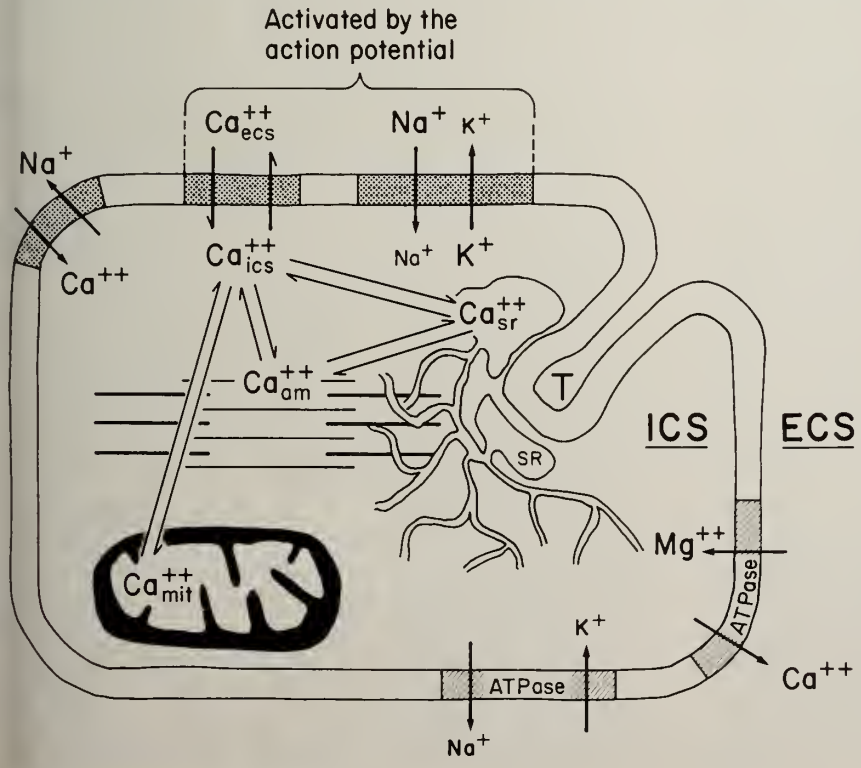

Figure 3—Physiochemical mechanisms affecting calcium ion fluxes in a myocardial cell. This schematic diagram of a myocardial cell shows the various calcium-related ion exchange mechanisms occurring at the plasmalemma and within intracellular organelles. ECS and ICS = extracellular and intracellular spaces, respectively; SR = sarcoplasmic reticulum; T = T-tubular system; Ca^{++}_{ecs}, Ca^{++}_{ics}, Ca^{++}_{am}, Ca^{++}_{sr} and Ca^{++}_{mit} refer to calcium in the extracellular and intracellular spaces, bound to actin-myosin filaments and within the sarcoplasmic reticulum and mitochondria, respectively; Na^+ = sodium, K^+ = potassium, Mg^{++} = magnesium and ATPase = adenosine triphosphatase.

calcium current; (2) exchangeable sarcolemmal and intracellular calcium stores; (3) calcium uptake and removal from the cytoplasm by the sarcoplasmic reticulum, mitochondria and across the sarcolemma, and (4) ion-exchange processes that indirectly affect calcium availability due to changes in the transmembrane balance of other ions—such as Na^+, K^+, H^+ and Mg^{++}.

The most consistent inotropic effect of the digitalis glycosides is an increase in the exchangeable free calcium pool without a detectable increase in total calcium content. The contraction-dependent calcium pool is enlarged by digitalis glycosides and correlates well with the inotropic effect, but occurs consistently only in contracting muscle and often has no effect in noncontracting muscle. This suggests that digitalis glycosides change the calcium-binding properties of the sarcolemma and intracellular membranes but only in the contractile state.

The critical problem is how digitalis glycosides bring about this change in calcium metabolism, and current experimental evidence points to an action through the fourth category mentioned above—that of indirectly altering calcium availability to the contractile elements by a direct effect on an ion-exchange process unrelated to calcium. Specifically, the direct inhibitory effect of digitalis glycosides on sarcolemmal Na^+-K^+ adenosine triphosphatase (ATPase) may indirectly influence calcium movement and contractile force by altering transmembrane gradients or intracellular pools of sodium or potassium. This theory is supported by a high degree of correlation between inotropic potency and Na^+-K^+ ATPase inhibitory potency of the glycosides.

Currently there is no evidence that therapeutic doses of digitalis glycosides alter the total intracellular content of either sodium or potassium, despite poisoning the Na^+-K^+ ATPase system that actively maintains the electrochemical gradients of these two monovalent cations. However, digitalis glycoside-induced phasic increases in intracellular sodium during the action potential without progressive intracellular accumulation of sodium have been postulated to stimulate a non-energy-dependent, sodium-calcium ion exchange across the sarcolemma, resulting in increased intracellular free calcium ions during each contractile cycle.[2] In addition, there is strong experimental evidence that at therapeutic concentrations digitalis glycosides increase the activity of an energy-dependent calcium pump in the sarcolemma for transporting calcium out of the cell, and this effect appears dependent upon digitalis glycosides binding to Na^+-K^+ ATPase.[3] This effect might act to maintain overall calcium balance and prevent progressive accumulation of intracellular calcium due to increased phasic sodium-calcium exchange. Precise documentation of these mechanisms has not been accomplished, and other theories relating Na^+-K^+ ATPase inhibition to inotropic effect have been proposed.[3,4]

Despite the lack of a complete understanding of the biochemical mechanism of action of the digitalis glycosides, the fact that the glycosides increase the force of contraction in isolated heart muscle under fixed loading conditions has been extrapolated to explain their beneficial clinical effects in congestive heart failure. Discouragingly, after several decades of clinical studies directed at proving that digitalis benefits patients with chronic heart failure, results have been variable and often contradictory (Table 1). In cases of heart failure with atrial fibrillation there is general agreement that digitalis is beneficial due to chronotropic effects that enhance ventricular filling and stroke volume. In chronic heart failure with sinus rhythm, the beneficial clinical effects of digitalis have been supported since 1919 by Henry Christian[5] and others,[6-9] but many of these studies were not controlled and involved patients with uncorrected hypertension, syphilitic heart disease and valvular heart disease. Since 1970, several studies have shown no long-term clinical benefit of digitalis in patients with heart failure in sinus rhythm, or lack of deterioration in clinical state on discontinuing maintenance therapy with digitalis.[10-14] The chief limitations of many of these studies are poorly defined heart failure populations and lack of randomized, controlled designs. A recent study with a prospective analysis of 24 patients with symptomatic chronic heart failure showed no change in symptoms, cardiothoracic ratio, left ventricular ejection fraction or duration of exercise a month after discontinuing maintenance digoxin therapy.[14] However, as with other studies, there was no control group or a crossover placebo control period.

Two available studies using a prospective, double-blind, placebo-controlled method have indicated that patients in chronic heart failure in sinus rhythm treated with digoxin do better clinically and show improvement in several indices of contractility and hemodynamic function.[15,16] The most recent of these studies using a clinicoradiographic heart failure score showed that heart failure was reduced by digoxin therapy in 14 of 25 outpatients in sinus rhythm, with 9 of the 14 responses being confirmed by either repeated trials (5 patients) or hemodynamic measurements by right heart catherization (4 patients).[16] The patients responding to digoxin therapy appeared to have more severe and more chronic heart failure than the nonresponders, larger end-diastolic dimensions by echocardiography and lower ejection fractions by radionuclide ventriculography, with the best predictor of a beneficial response to digoxin being the finding of a third heart sound. The authors postulated that patients who continue to have higher left atrial pressures and left ventricular dilatation despite diuretic therapy—hence more likely to have a third heart sound—represent a group more likely to respond to digoxin due to a difference in the underlying mechanism of their left ventricular failure. This theory awaits further testing, but the results of this study show unequivocally that long-term digoxin use is beneficial in some patients with chronic heart failure in sinus rhythm.

The direct inotropic effect of digitalis in humans has been shown in exposed hearts at cardiopulmonary bypass, but in patients with chronic heart failure, the assessment of inotropic effect has been limited to indirect measures using various indexes of contractility such as systolic time intervals, rate of rise of ventricular pressure and end-systolic pressure-volume curves. Although many of these indexes of contractility are improved by digitalis in heart failure patients, overall left ventricular pump function (filling pressures and cardiac output) after administration of digitalis has been variable. In hemodynamic studies done before 1962, most showed a definitely increased cardiac output, reduced mean pulmonary artery pressure or decreased right ventricular end-diastolic pressure after digitalis use in chronic heart failure patients. However, as many as a third of patients in these early hemodynamic studies showed no improvement in

cardiac output immediately following treatment with digitalis. Recent studies have also shown the variability of hemodynamic responses to digitalis therapy in cases of chronic heart failure[16,17] and suggest that further investigation will be necessary to develop better predictors of initial and lasting hemodynamic improvement in these patients.

Diuretic agents have been studied mostly in cases of acute heart failure and produce a reduction in left ventricular filling pressure and cardiac output. In cases of chronic heart failure hemodynamic effects of diuretics have been less well studied, but again appear to be beneficial by lowering filling pressures without clinically significantly reducing cardiac output. The effect on the pressure-volume relationship is to reduce end-diastolic volume and hence stroke volume without major changes in systolic pressure (reverse of Frank-Starling reflex) (Figure 4). Clinically, diuretics clearly diminish dyspnea and edema in heart failure, but whether they improve mortality or the natural history of the disease is unknown.

Vasodilators have been studied extensively in cases of both acute and chronic congestive heart failure[18] and have different effects on the pressure-volume relationship and left ventricular function depending on the relative degree of venodilator versus arterial dilator potency. The venodilators (nitroglycerin, isosorbide dinitrate, prazosin hydrochloride) produce great reductions in left ventricular filling pressure with modest improvement in cardiac output, while arterial vasodilators (phentolamine hydrochloride, hydralazine hydrochloride, minoxidil) produce less dramatic reductions in filling pressures and greater increases in cardiac output due to decreased impedance to ejection (Figure 5). The overall effect of these agents on the pressure-volume relationship, though to variable degrees depending on the properties of the vasodilator, is reflected as a primary reduction in early, peak and late systolic pressures resulting in increased stroke volume, hence the term afterload reduction. The new end-systolic pressure-volume point falls on the curve previously defined by the baseline contractile state, indicating that contractility is not directly increased by these agents. End-diastolic volume usually decreases mildly to moderately, depending on the degree of venodilator potency of the agent and degree of improvement in cardiac output.

The vasodilators widely used in clinical practice (hydralazine, isosorbide, prazosin) all have some degree of overlap in arterial and venous vasodilator effect, and many investigators have recommended the combined use of arterial and venous vasodilators for the benefits of both reduced arterial impedance and lowered left ventricular filling pressures. This represents an effort to achieve with oral vasodilators the greatly beneficial hemodynamics produced by sodium nitroprusside, an efficacious arterial and venous vasodilator administered intravenously for the treatment of acute left ventricular failure.

The angiotensin converting-enzyme inhibitors produce

TABLE 1.—*Summary of Clinical Studies on the Efficacy of Digitalis in Patients with Congestive Heart Failure With Sinus Rhythm*

Study, yr	*Patients in NSR Number*	*Pathologic Features*	*Duration of Study*	*Controlled*	*Variables Assessed*	*Conclusions on Digitalis Therapy*
Christian, 1919[5]	3	Hypertension, idiopathic	1 wk-2 yr	No	Symptoms, urine output	Beneficial
Marvin, 1927[6]	20	Rheumatic, syphilis, atherosclerosis	1-4 mo	No	Symptoms, edema, weight loss	Beneficial except in rheumatic cases
Harrison et al, 1931[7]	43	Hypertension, syphilis, atherosclerosis	Not reported	No	Symptoms only	Usually beneficial (85% of cases)
Gavey and Parkinson, 1939[8]	65	Hypertension, syphilis, atherosclerosis	1-2 wk	No	Symptoms, urine output, weight loss	Usually beneficial (60% of cases)
Sokolow et al, 1942[9]	4	Hypertension, atherosclerosis	7-15 mo	No	Symptoms, venous pressure, weight loss, vital capacity	Harmful if withdrawn; beneficial when given
Davidson and Gibson, 1973[10]	9	Post-valve replacement	10 days	No	Systolic time intervals	Beneficial initially; no effect long-term
Hull and Mackintosh, 1977[11]	18	Not reported	3 mo	No	Symptoms and signs	No harmful effect of withdrawal in 17/18 patients
McHaffie et al, 1978[12]	6	Myocardial infarction, idiopathic	3 mo	No	Submaximal exercise	No improvement over use of diuretics alone
Johnston and McDevitt, 1979[13]	56	Ischemia, valvular, hypertension	3 mo	No	Symptoms and signs	No harmful effect of withdrawal in 86% of patients
Dobbs et al, 1977[15]	33	Ischemia, rheumatic, emphysema, hypertension	3 mo	Yes (Placebo cross-over)	Symptoms, signs and systolic time intervals, spirometry	Deterioration on change to placebo
Gheorghiade and Beller, 1983[14]	24	Ischemia	1 mo	No	Symptoms, signs, CXR, LVEF, exercise	No harmful effects of withdrawal
Lee et al, 1982[16]	25	Ischemia, idiopathic, hypertension	2 wk-7 mo	Yes (Placebo cross-over)	Symptoms, signs, CXR, spirometry, phono, echo, RVG, cath	Definite benefit in 14/25 patients; responders had worse CHF, lower ejection fraction and more often S_3 than nonresponders

NSR = normal sinus rhythm, CXR = chest x-ray, LVEF = left ventricular ejection fraction, phono = phonocardiogram, echo = echocardiogram, RVG = radionuclide ventriculogram, cath = cardiac catheterization, CHF = congestive heart failure, S_3 = third heart sound

hemodynamic effects in heart failure more similar to pure arterial vasodilators, but also greatly increase venous capacitance and reduce right atrial and left ventricular filling pressures. The hemodynamically beneficial effects of converting-enzyme inhibitors are most pronounced in patients with the highest pretreatment plasma renin activity and hyponatremia, and, like other vasodilators, also result in reducing sympathetic activity reflected as decreased plasma norepinephrine concentrations.

Clinically, dyspnea, fatigue, exercise tolerance and overall functional heart classification improve both immediately and over the long term in many patients treated with vasodilators. However, limitations for their use occur frequently due to initial hypotension and attenuation of the hemodynamic effects (tolerance) with ongoing use (Table 2). For the converting-enzyme inhibitors both early and late tolerances are well described, and hemodynamic or biochemical markers are of limited value in predicting which patients will respond on a long-term basis. As many as a third of patients treated with captopril who respond initially will have either fluctuating or permanently attenuated responses, and of those who do not respond at first, up to a third may show a delayed response.[19]

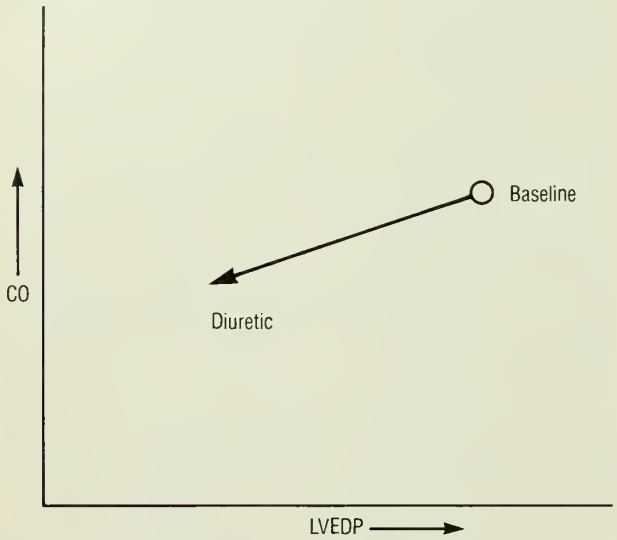

Figure 4.—Effects of diuretics on ventricular function in congestive heart failure. This schematic of the effect of diuretics on the relationship between cardiac output (CO) and left ventricular end-diastolic pressure (LVEDP) shows that there is a pronounced reduction in LVEDP with a mild decrease in CO. See text for further discussion.

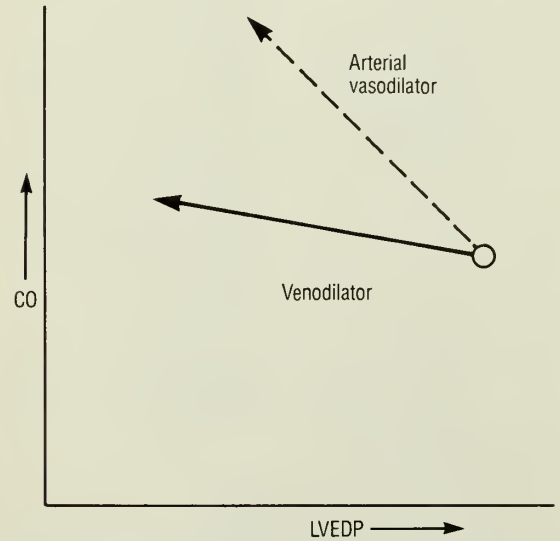

Figure 5.—Effect of vasodilators on ventricular function in congestive heart failure. This schematic of the effect of vasodilators on the relationship between cardiac output (CO) and left ventricular end-diastolic pressure (LVEDP) shows that venodilators reduce LVEDP dramatically with insignificant changes in CO, whereas arterial vasodilators produce greater increases in CO with less effect on LVEDP. See text for further discussion.

TABLE 2.—*Limitations of Vasodilator Therapy*

Side effects
Hypotension
Varying initial and long-term response rates with poor predictors of response
Attenuation of acute hemodynamic effects with long-term therapy (tolerance)

Despite these limitations, a recent multicenter, randomized, placebo-controlled trial of captopril in cases of chronic CHF has shown that captopril can produce symptomatic improvement and increased exercise capacity after 12 weeks of therapy.[20] The study included 92 patients randomly assigned to receive either captopril (49) or placebo (42), and included New York Heart Association (NYHA) functional class II and III patients. Most of the captopril patients (61%) showed symptomatic improvement compared with only 24% of the placebo-treated group, and left ventricular ejection fraction and exercise durations were both significantly better in the captopril group compared with the placebo group. This large study represents one of the first of its kind in assessing a therapeutic agent in chronic CHF and suggests that captopril and other converting-enzyme inhibitors may be the most efficacious agents at present for long-term treatment of CHF.

The New Inotropes

Intravenous and Oral Sympathomimetic Agents

Variable responses to digitalis and limitations of vasodilator therapy have encouraged the development of new agents that can more consistently and predictably improve left ventricular pump function in cases of heart failure. Further development of more potent vasodilators has not proved beneficial due to the limitation of hypotension and the expectation of only marginally increased cardiac output with further reductions in systemic vascular resistance by more potent agents. However, much effort has been devoted recently to the development of more potent and reliable inotropic agents in hopes of increasing contractility and cardiac output without excessive increases in myocardial oxygen consumption.

Because of the known inotropic effects of the sympathomimetic amines, epinephrine and norephinephrine, the first agents to be developed were the intravenously and then orally administered β-adrenergic agonists (Table 3). Many of the cardioactive β-agonists that augment myocardial contractility have been used intravenously in cases of acute and chronic heart failure, but are limited by side effects and the lack of an oral analog for ongoing administration. Norepinephrine increases contractility and inotropic state in left

TABLE 3.—*Intravenous and Oral Sympathomimetic Amines*

Route of Administration	*β_1-Agonists*	*β_2-Agonists*	*Nonselective*
Intravenous	Dopamine hydrochloride* Dobutamine hydrochloride*	Isoproterenol hydrochloride	Isoprenaline hydrochloride Norepinephrine Epinephrine
Oral	Prenalterol hydrochloride	Pirbuterol hydrochloride Salbutamol (albuterol) Terbutaline sulfate	

*Significant overlap in β_1- and β_2-agonist effects.

ventricular failure, but may also increase systemic vascular resistance limiting the increase in cardiac output, and greatly increase myocardial oxygen demand by increasing heart rate and afterload. Isoproterenol hydrochloride induces a pronounced increase in cardiac output, but also reduces diastolic arterial pressure, increases heart rate and produces myocardial irritability.

Dopamine hydrochloride and dobutamine hydrochloride, two relatively nonselective β-adrenergic agonists, have proved beneficial in cases of refractory congestive heart failure for short-term intravenous infusion. Dopamine at low doses increases contractility via β-receptor stimulation, improves cardiac output without significant changes in heart rate or myocardial oxygen consumption, reduces systemic vascular resistance, increases renal blood flow and improves renal sodium excretion. At higher doses, it increases heart rate, arterial pressure and end-diastolic pressure by increased stimulation of β-and α-adrenoreceptors, and in some patients with heart failure increased filling pressures and pulmonary congestion may develop even at lower doses.

Dobutamine appears especially beneficial for the treatment of severe heart failure in that it selectively increases myocardial contractility without inducing any significant chronotropic or peripheral vascular effects. A reduced left ventricular filling pressure occurs with a simultaneous pronounced increase in cardiac output in the absence of changes in heart rate, suggesting a direct inotropic effect.[21] When compared with dopamine, dobutamine produces a similar increase in cardiac output but with less increase in arterial pressure and a greater decrease in systemic vascular resistance. Hence, for short-term infusion in patients with refractory heart failure associated with hypotension, dopamine may be preferable to dobutamine, whereas dobutamine would be preferable in a setting of high systemic vascular resistance and normal arterial pressure. Both agents, however, are limited to short-term intravenous use for the initial treatment of cases of worsening pump failure.

The combined use of dopamine or dobutamine with vasodilator agents, particularly nitroprusside and nitroglycerin, has been shown to result in more favorable hemodynamic responses than achieved with the inotropic or vasodilator drugs administered separately. The reduction in arterial impedance to left ventricular ejection by the vasodilators, coupled with a direct increase in contractile force by the inotropes, allows for a synergistic effect of the two mechanisms to improve cardiac output and overall left ventricular performance. The doses of these intravenous inotropic and vasodilator agents can be titrated carefully to achieve the optimal balance of effects for each patient.

Can these intravenously administered sympathomimetic agents be of any lasting benefit to patients with chronic heart failure? Certainly if an acute decompensation of left ventricular function can be reversed by these agents, allowing conventional oral therapies to regain control of ventricular function once an equilibrium is reestablished, immediate death may be prevented and many patients may return to their previous level of function. In addition, there is increasing evidence that short-term infusions of dobutamine in congestive heart failure may confer a sustained beneficial hemodynamic and clinical effect lasting up to several months, and may be similar to the effects of exercise conditioning on left ventricular function.[22,23] A recent randomized, controlled study showed a sustained improvement for four weeks in the functional state of patients with congestive cardiomyopathy treated with a 72-hour infusion of dobutamine, as well as improvement in left ventricular ejection fraction and velocity of circumferential fiber shortening at rest.[22] Exercise tolerance was also significantly improved, but total body oxygen consumption was reduced both at rest and during exercise after administration of dobutamine. The explanation for the sustained postinfusion benefits has not been established, but ventricular biopsy studies have shown improvement in myocardial ultrastructural morphology and in the level of high-energy phosphates after intermittent inotropic therapy.

The search for an effective orally active β-adrenergic agonist in the management of chronic heart failure has at the present time not yielded an agent with consistent long-term clinical and hemodynamic benefits. Salbutamol (albuterol) and pirbuterol acetate, selective β_2-agonists, appear to have both inotropic and vasodilator actions in patients with chronic congestive heart failure. The magnitude of each of these actions is difficult to assess due to a reflex reduction in systemic vascular resistance that occurs with improved cardiac output and vice versa. Salbutamol, however, has positive inotropic properties in isolated rabbit papillary muscles and pirbuterol increases the rate of rise of left ventricular pressure in dogs. Acute hemodynamic effects of salbutamol in patients with chronic heart failure show primarily pronounced decreases in systemic vascular resistance, increases in heart rate and increases in cardiac output, with minimal effects on left ventricular filling pressure and no significant changes in blood pressure. Pirbuterol produces similar acute hemodynamic effects but with insignificant effects on heart rate, thus being perhaps safer than salbutamol for long-term therapy due to a lesser

increase in myocardial oxygen demand and lower risk of ventricular irritability.

Long-term administration of pirbuterol to patients with severe heart failure has been found in several studies to have limited success due to attenuation of hemodynamic and clinical effects. A recent double-blind, randomized, seven-week trial comparing pirbuterol (20 mg given three times a day) with placebo in 12 patients showed no improvement in clinical state, exercise tolerance, maximal oxygen uptake, echocardiographic left ventricular dimensions or cardiothoracic ratio by pirbuterol.[24] However, other studies have shown sustained beneficial effects when measured as left ventricular ejection fraction at six weeks of therapy,[25] or repeated right heart catheterization in a larger group of patients (29) at three months.[26] Despite overall changes toward hemodynamic improvement in the latter study, there was a great deal of individual variation in response and no reliable predictors to separate responders from nonresponders.

Several possibilities exist to explain the diverse responses to pirbuterol in chronic heart failure. First, "down regulation" of myocardial and vascular smooth muscle β-receptors may occur with ongoing β-agonist therapy as suggested by a study showing diminished density of β-receptors on lymphocytes from patients treated on a long-term basis with pirbuterol.[27] Second, intrinsic myocardial failure may be worsening at different rates in different patients, some deteriorating faster than the cardioactive effects of the β-agonist can maintain function. Third, the β-agonist properties of pirbuterol may selectively alter regional blood flow in a detrimental fashion such that flow is directed away from exercising muscles to other dilated vascular beds.

Prenalterol hydrochloride represents the most extensively studied orally active β_1-adrenoreceptor agonist for the treatment of chronic heart failure. Initially, prenalterol increases cardiac index and in most studies also heart rate, with mild to moderate decreases in systemic vascular resistance and left ventricular filling pressures and insignificant changes in blood pressure. Despite encouraging early results of short-term (one week) follow-up in patients treated with prenalterol, two recent controlled, randomized, double-blind studies of prenalterol in the ongoing treatment (two weeks to six months) of severe congestive heart failure have shown no sustained benefit by either hemodynamic or clinical measurements.[28,29] One of these studies showed a sustained increase in heart rate on prenalterol despite attenuation of cardiac index and other hemodynamic features, suggesting that "down regulation" of β_1-receptor responsiveness did *not* occur in this group of patients.[28] However, the other recent long-term study showed no change in heart rate along with the absence of changes in other hemodynamic values, but did show a significant reduction in heart rate response to exercise in the heart failure patients on a regimen of prenalterol.[29] These investigators suggest that the blunted exercise heart rate response represented either a down regulation of cardiac adrenoreceptors or a partial β-antagonist effect not seen with short-term administration.

In summary, the currently studied orally active sympathomimetic amines show beneficial acute hemodynamic effects consistent with combined inotropic and vasodilator actions in patients with chronic congestive heart failure. However, long-term benefits of ongoing oral therapy with pirbuterol and prenalterol have been limited. Chronic adaptations of adrenergic responsiveness of the heart to prolonged sympathetic stimulation, both as part of the hyperadrenergic state of heart failure and as a response to long-term exposure to exogenous β-agonists, may limit the potential of even highly selective and potent β-adrenergic drugs in the treatment of chronic congestive heart failure.

TABLE 4.—*New Nonglycosidic, Nonsympathomimetic Inotrope-Vasodilator Agents*

Amrinone	MDL 19,205
Milrinone	RO13-6438 (posicor)
MDL 17,043	AR-L115BS (sulmazol)

Nonglycosidic, Nonsympathomimetic Inotrope-Vasodilator Agents

In 1978 a new class of inotropic vasodilator agents was developed that produced an increase in myocardial contractility without acting through any previously described pharmacologic mechanism.[30] The first of these was *amrinone*, a bipyridine derivative, which increased papillary muscle force of contraction in a dose-dependent fashion, not inhibited by ouabain (a digitalis glycoside), propranolol hydrochloride (a β-blocker), metiamide (histamine-2-receptor agonist), atropine oxide hydrochloride or reserpine.[31] In addition, amrinone did not alter myocardial norepinephrine content of Na^+-K^+ ATPase activity and produced a *direct vasodilator effect* on animal hind limb. Hence, in addition to potent inotropic effects, amrinone also caused vasodilation, both by unknown mechanisms but both theoretically beneficial for the treatment of CHF. Since that time many other agents with similar effects have been developed, including milrinone (an amrinone analog with 20 times the in vitro potency), MDL 17,043, MDL 19,205, posicor and AR-L115BS (sulmazol) (Table 4).

Acute hemodynamic effects of these agents in the treatment of CHF include *pronounced dose-dependent increases in cardiac index and stroke work index and substantial decreases in left ventricular filling pressure, mean pulmonary artery pressure and right atrial pressure,* with insignificant effects on mean arterial pressure or heart rate.[32,33] Myocardial metabolic effects have shown, in general, reduction in myocardial oxygen consumption at rest and no adverse effect on myocardial lactate extraction. These changes reflect both inotropic and vasodilator effects and are highly reproducible even in patients with severe CHF who are refractory to maximum vasodilator therapy.

Phase II uncontrolled clinical studies have shown sustained hemodynamic and clinical responses to these agents with ongoing therapy.[34–37] However, with the use of amrinone and milrinone it has been shown that although beneficial hemodynamic responses occur both immediately and with ongoing treatment, there is substantial progression of the underlying disease as evidenced by worsening baseline hemodynamic indexes after drug withdrawal. In a recent study, milrinone was given for 2 to 15 weeks to seven patients with severe CHF and produced increases in cardiac index and decreases in pulmonary capillary wedge pressure both at initiation of therapy and at follow-up study.[36] Long-term symptomatic improvement occurred in five of the seven pa-

tients and there were no adverse side effects of therapy. However, clinical improvement was sustained in only two patients despite persistent beneficial hemodynamic effects in all patients. Withdrawal of milrinone therapy resulted in hemodynamic deterioration in all patients, with a significant decrease in stroke volume index despite no significant change in pulmonary capillary wedge pressure. Hence, in initial uncontrolled studies, hemodynamic responses appear to be sustained but symptomatic improvement is variable.

Similar results have been reported with long-term amrinone therapy, but adverse side effects have been more frequent. The most common side effects of amrinone, the agent most extensively studied at present, include gastrointestinal symptoms (nausea, diarrhea, anorexia), thrombocytopenia and neurologic symptoms (dizziness, lightheadedness and headache). These have been common and severe, and have limited its long-term use. A recent study of 13 patients treated on a long-term basis with amrinone showed no resolution of heart failure symptoms, nor improved noninvasive indexes of left ventricular function (echocardiography and systolic time intervals) or exercise ejection fraction, although exercise duration was enhanced when compared with that of a control group of ten patients.[38] In this study there was a high incidence of side effects and the authors concluded that the low benefit-to-risk ratio did not warrant widespread application of amrinone in the treatment of CHF.

Recently, the results of the first large randomized, placebo-controlled study of amrinone in outpatients with chronic CHF have been reported.[39] This multicenter study included 173 patients with CHF treated on a long-term basis with amrinone given orally. Patients were classified as NYHA functional class II (40%), class III (59%) and class IV (1%) and had a mean left ventricular ejection fraction of 25%. After 12 weeks of amrinone therapy during which "responders" were separated from "nonresponders" on the basis of exercise capacity, the "responders" were randomly assigned in double-blind fashion to either continue an amrinone regimen or be switched to placebo for another 12 weeks of therapy. There was no difference in exercise capacity, episodes of worsened CHF severe enough to terminate treatment, symptom score or NYHA class between amrinone and placebo-treated groups, and adverse effects were more common in the amrinone-treated group. Another recently completed multicenter, randomized and controlled study of long-term therapy with amrinone given orally in 99 patients with NYHA class III or class IV CHF has also shown lack of clinical efficacy of amrinone with ongoing therapy, even in a subgroup of patients who were able to tolerate maximum doses without limiting adverse side effects.[40] Hence, it appears that long-term inotropic therapy with amrinone will not prove efficacious, in part due to its poor therapy-to-toxicity ratio. Currently there is no information from placebo-controlled trials regarding long-term treatment of CHF with milrinone, although its lower adverse side-effect profile may make it more suitable for detecting beneficial clinical responses during long-term therapy.

Summary

The syndrome of congestive heart failure results from a primary loss of contractile function of the myocardium, leading to diminished stroke volume, cardiac output and arterial pressure. Reflex compensatory mechanisms of the cardiovascular system include the Frank-Starling reflex, increased sympathetic activity, salt and water retention and, finally, myocardial cell hypertrophy. These compensatory responses are initially beneficial, but ultimately lead to the adverse symptoms and signs of congestive heart failure. Therapeutic strategies have included inotropic support with digitalis glycosides, reducing systemic and pulmonary venous congestion with diuretics and unloading of left ventricular ejection with vasodilators. For ongoing therapy the angiotensin converting-enzyme inhibitors, specifically captopril, appear to produce the most beneficial long-term clinical responses in recent controlled studies. Digitalis, diuretics and vasodilators have many limitations in the treatment of heart failure, the most challenging of which is the wide variability of response rates for individual patients. The new oral inotropic agents have beneficial hemodynamic effects in patients with severe heart failure for whom other therapies have failed, but at the present time have not been shown in controlled studies to produce clinical improvement with long-term therapy.

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Epitomes

Important Advances in Clinical Medicine

Orthopedics

The Scientific Board of the California Medical Association presents the following inventory of items of progress in orthopedics. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, research workers or scholars to stay abreast of these items of progress in orthopedics that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Orthopedics of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to Division of Scientific and Educational Activities,
California Medical Association, 44 Gough Street, San Francisco, CA 94103

Ischemic Necrosis of the Femoral Head

THE CAUSE of ischemic necrosis of the femoral head is unknown except in displaced fractures of the femoral neck, Gaucher's disease and decompression sickness (air embolism). This disorder occurs frequently in patients with alcoholism and those who have had large doses of corticosteroids. The cause is controversial although there is some evidence that alcohol and steroids produce fat cell and fat metabolism aberrations that affect and encroach on the intramedullary vascular system, thus producing an avascular area in the femoral head. In many cases the necrosis is idiopathic.

Diagnosis depends on taking a careful history and the results of a physical examination and x-ray evaluation. Supportive evidence may be supplied by radioisotopic scanning and laminography. Frequently radiographic findings are inconclusive so that diagnosis will depend on the results of a careful dynamic pressure study and core biopsy.

Treatment is based on the six-stage classification of Marcus and others. Stages V and VI are essentially the same and can be combined. In stages I and II, core biopsy with decompression or bone grafting techniques are effective in more than 85% of cases. These surgical procedures are not satisfactory in later stages, during which replacement arthroplasty, osteotomy and osteochondral allografts are more viable options. Electrical stimulation has been advocated recently as a promising technique for treatment; however, the evidence to support this suggestion is at best weak.

Until the cause of femoral head osteonecrosis has been clarified and preventive treatment devised, a surgical procedure is the best available treatment. Early recognition and surgical treatment during stages I and II offer the best hope for salvaging a diseased femoral head. Osteotomy and allograft techniques may prove successful during the advanced stages (III and IV), but failure of these procedures will necessitate a replacement operation, which is less than ideal.

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Myocutaneous Flap for Soft Tissue Reconstruction

THE MYOCUTANEOUS FLAP has become a versatile and safe procedure for soft tissue reconstruction. If done properly, it provides skin and soft tissue coverage with tissue that has a rich blood supply, a large and long vascular pedicle and highly predictable anatomy. The technique is especially useful in covering the large areas of skin and soft tissue lost following trauma, infection, tumor resection or in scarred or irradiated recipient beds. In addition to wound coverage, myocutaneous flaps are useful to restore form, contour and function.

Myocutaneous flaps have been used in a number of ways. (1) A flap can be raised, leaving its vascular pedicle attached. The flap can then be rotated to cover an adjacent defect without interruption of its blood supply. An example of this is a latissimus dorsi myocutaneous flap rotated to cover a posterior midline exposed Harrington rod. (2) The muscle alone can be transferred with its blood supply if the addition of the overlying skin and fat will make the flap too bulky. In this case a split-thickness skin graft is placed over the muscle belly. (3) With the development of microvascular techniques it is possible to transfer a free vascularized muscle or myocutaneous flap to a distant wound in one stage. An example of this is using a free vascularized latissimus dorsi flap to cover an open

femur or tibia fracture that has an extensive soft tissue defect. Besides providing coverage, free gracilis muscle or myocutaneous flaps have been used successfully to provide active finger flexion or extension in Volkmann's ischemic contracture by suture of the nerve supply of the gracilis to the appropriate motor nerve of the recipient site.

A clinician needs detailed knowledge of the vascular anatomy and patterns of blood supply to the muscles and their limitations to treat wounds by a myocutaneous flap procedure.

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Complications of Chemonucleolysis

CHYMOPAPAIN WAS APPROVED for clinical use in the United States for the treatment of herniated lumbar discs on November 10, 1982. Currently, two products are available: Chymodiactin (Smith) and Discase (Baxter-Travenol).

Experience of more than 80,000 injections has proved chymopapain to successfully relieve radicular pain in 75% of cases (range 62% to 90%). Minor problems with chemonucleolysis include a failure rate of approximately 25% and transient worsening of back and leg pain after the injection. Major complications include potentially fatal anaphylaxis, neurologic risk and septic discitis.

Allergic complications of chemonucleolysis range from pruritus or urticaria to fatal anaphylaxis. The overall incidence of anaphylaxis is 0.5%, with 0.3% in men and 0.9% in women. When the enzyme is given with local anesthesia the overall incidence of anaphylactic reactions is 0.4%—0.2% in men and 0.7% in women. With general anesthesia, the overall incidence is 0.6%, with 0.4% of men and 1.0% of women given the chemonucleolytic agent experiencing anaphylaxis. The onset of 96% of anaphylactic reactions is within 20 minutes of injection. Of those patients who have had a reaction to a test dose alone (theoretically the most sensitive group), 94% experienced reactions within ten minutes. There have been no deaths caused by anaphylaxis in patients under local anesthesia. The role of serologic determinations of IgE antibody to chymopapain and skin-testing methods is currently under investigation. False-negative results of serologic testing have occurred, and thus vigilance remains essential.

To lessen the risk of anaphylaxis, physicians should observe certain precautions. Patients with a known sensitivity to chymopapain, papaya or its derivatives or to a previous chymopapain injection should not be given the drug. An intradiscal test dose of 0.2 ml of chymopapain followed by a 10- to 15-minute observation period is recommended. Patients who have concurrent medical conditions that include cerebrovascular and cardiovascular disease, which could compromise successful resuscitation, should not be given chymopapain. Pretreatment with histamine (H_1 and H_2) antagonists including diphenhydramine hydrochloride and cimetidine is recommended. Prompt recognition and aggressive treatment of suspected anaphylaxis with epinephrine and intravenous administration of fluids is essential.

Neurologic reactions including cerebral hemorrhage, sudden onset of paraparesis or paraplegia, transverse myelitis and other neurologic complications have been reported. Because technical factors including subarachnoid injection of radiographic contrast or chymopapain, or both, have been implicated, avoidance of discographic procedures and meticulous technique are essential.

Transverse myelitis has been reported after chemonucleolysis at an incidence of 1 per 18,000. The spontaneous incidence of transverse myelitis has been reported as approximately 1 per 100,000 person-years. These patients have a delayed onset of paraparesis or paraplegia—about two or three weeks postinjection—without prior signs or symptoms. Some researchers suggest that delayed hypersensitivity of immune complex disease is caused by chymopapain or antigenic breakdown products of the nucleus pulposus but these theories remain unproved.

Discitis, both aseptic and septic, has been reported. Septic discitis is usually staphylococcal; meningitis and death complicating septic discitis have been reported, so meticulous attention to sterile technique is essential.

Although successful in 75% of cases, chemonucleolysis is associated with remote but significant risks. Proper patient selection, meticulous technique, prompt recognition and treatment of complications and thorough informed consent are essential.

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Electrical Stimulation of Ununited Fractures

ELECTRICAL STIMULATION of ununited fractures is now an accepted technique available to all orthopedic surgeons. Some of the causes of delay or nonunion of fractures are apparent, including infected fractures, fractures with a significant gap and severe open fractures with major soft tissue loss. Nonunions can occur, however, in young, healthy persons who sustain a closed fracture with minimal displacement.

Grafting the unhealed site with bone from the iliac crest has been the conventional method to promote healing. Rigid fixation using internal or external metal devices also has a high rate of success, but these procedures carry a risk of infection and may be unsuccessful even after several attempts. Electrical stimulation is an alternative that is effective and the newer forms have few risks.

The following three techniques of electrical stimulation are available: (1) totally invasive: the electrode is embedded in the fracture site during an open surgical procedure; (2) semi-invasive: under local anesthesia in the operating room, small stainless steel wire electrodes are placed percutaneously into the fracture site, and (3) noninvasive: the technique of

inductive coupling using large electromagnetic coils to induce an electrical field at the nonunion site.

There are disadvantages to these techniques: healing may take up to six months in large bones and patients may not bear weight for at least the first three months of treatment. All procedures but the noninvasive coil electrodes have a risk of infection.

A new type of noninvasive electrical stimulation using capacitive coupling is in its final stages of patient testing. In capacitive coupling, an electrical field is induced in bone by small stainless steel electrodes placed on a patient's skin at the nonunion site. The device is powered by a 9-V battery attached to the outside of the cast allowing the patient to move about freely. This is an office procedure, and the patient may bear weight as tolerated during the course of treatment.

These electrical stimulation techniques are reported to be successful in 70% to 80% of cases, but the rate varies with the location of the nonunion. Nonunion of the tibia responds to electrical stimulation—more than 90% of patients heal completely, whereas nonunion of the humerus responds very poorly. Humeral nonunions frequently develop a synovial pseudarthrosis (false joint) consisting of a fluid-filled sac between the fracture fragments. This allows gross motion at the nonunion site and should be treated by surgical removal of the synovial sac, rigid fixation and bone grafting. If this treatment fails, electrical stimulation may be successful once the nonunion has been well stabilized.

At the present time there is no clear evidence that electrical stimulation is effective in treating fresh fractures, nor that adding this treatment to conventional bone grafting will significantly increase the chance of healing.

Bone grafting and rigid fixation by either external or internal devices are still acceptable techniques and have an equal or slightly higher success rate when compared with electrical stimulation. However, all require a surgical procedure with the accompanying risk of infection.

Electrical stimulation is a safe and effective addition to the procedures available to orthopedic surgeons for the treatment of unhealed fractures.

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Management of Major Pelvic Ring Fractures

FRACTURES OF THE PELVIS can be divided into minor and major ones. The minor fractures include avulsions and those that ostensibly only disrupt the pelvic ring at one point. Major fractures involve the pelvic ring at two or more diametric positions and may be stable or unstable. Most fractures caused by shearing forces, some caused by anteroposterior compression and occasionally those caused by lateral compression are unstable.

Instability is suggested by a patient's history, physical examination and by the results of special radiologic examinations. Anteroposterior and 45-degree inlet and outlet radiographs of the pelvis are essential. Cephalad migration of one hemipelvis, fracture of the fifth lumbar transverse process and avulsion fractures of the ischium and ischial spine all suggest instability. The possible points of pelvic ring disruption include the sacrum, sacroiliac joint, ilium, acetabulum, pubic arches and symphysis pubis. Computed tomography is often helpful in confirming the clinical and plane radiographic impression and assists in planning therapy.

The time-honored treatment of pelvic fractures with slings and traction is now rarely indicated and may in fact be detrimental in unstable fractures caused by lateral compressive forces. The pelvic sling is usually uncomfortable, makes nursing difficult, prolongs hospital stay and often will not achieve a good reduction or stabilization.

Recent advances in external and internal fixation techniques have greatly improved the capability to deal with the unstable pelvic fracture. A simple tie-beam arrangement with two Schanz type pins in each anterior iliac crest region connected by rods stabilizes anterior disruptions when the posterior sacroiliac interosseous ligaments are intact. More massive external fixators with pins above and below the anterior superior iliac spine may be used for the Malgaigne type fracture. However, the emphasis has recently been placed more on internal fixation with screws, rods or plates posteriorly combined with double plating of the symphysis pubis or a simpler frame anteriorly.

The advantages of external fixators and internal fixation techniques include better stabilization, improved control of pain and bleeding, easier nursing and shorter hospital stay.

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Tile M, Pennal GF: Pelvic disruption: Principles of management. Clin Orthop 1980 Sep; 151:56-64

External Fixation of Tibia Fractures

MANAGEMENT of a severe open tibia fracture with extensive soft tissue injury continues to pose a therapeutic dilemma for most orthopedic surgeons. Although external fixation has been practiced for centuries, the renewed interest in this treatment has led many orthopedists to review and modify their fracture management protocols. The classic "pins and plaster" technique is a modification of the external fixation system. The lack of accessibility to the wound, unstable pin fixation, inability to reset the fracture if necessary and bulky casts have led trauma surgeons to search for a more rigid, low profile, external fixation system.

Although there are many variations on a theme, external fixation frames are basically designed for one-plane or two-plane fixation, depending on the stability of the fracture. Less rigid frames consisting of one-plane or half-pin anterolateral frames are indicated in the open type II or III tibia fracture with minimal comminution and minimal soft tissue involvement. On the other hand, two-plane frame fixation, as shown by the quadrilateral or the Delta frame, is indicated for severe open fractures of the tibia where there is segmental bone loss, severe comminution or massive soft tissue injury. The key

difference is that one-plane frame fixation provides less stability than the two-plane or Delta frame fixation configuration.

Tibia external fixation is technically facilitated by the use of C-arm fluoroscopy and a radiolucent table extender. This technique preserves precious intraoperative time that is otherwise lost awaiting development of the roentgenograms. Occasionally stability is enhanced by one or two strategically placed intrafragmentary compression screws that provide temporary rotational control, length and reduction while the external frame is being constructed. After the operation, dorsiflexion foot splints should be applied to prevent equinus deformities. Fastidious care of the pin should be instituted and the leg should be elevated to prevent edema during the early phases of treating the wound.

Prolonged immobilization of patients has been implicated in nonunions of the tibia treated with external fixation. A recent review of tibia fractures treated at the University of California, Davis, Medical Center in Sacramento suggests that a brief period of external fixation—six to eight weeks—followed by early bone grafting and the use of weight-bearing casts has resulted in high rates of union and few pin tract complications. This temporal relationship provides maximum soft tissue benefit and does not jeopardize bone union.

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Management of Long Bone Fractures With External Fixators

In recent years external fixation has become the treatment of choice in the management of type III fractures of long bones. The advantages of rigid external fixation in these injuries is that it allows for complete visualization of the soft tissues, ease of inspection and accessibility and allows for repeated debridements without removal of cumbersome dressing and plaster casts.

In addition to the tibia, we have found external fixation useful in the management of fractures of the femur that involve considerable soft tissue and bony injury, when intermedullary fixation is not appropriate or not possible. External fixation allows the patient to return easily to the operating room for wound debridement and delays primary closure or skin-grafting or both until the appropriate time.

External fixation can be used in type III injuries of the humerus and forearm when there is extreme soft tissue destruction and bony loss. Many of these injuries are associated with close-range bullet wounds, which cause extensive comminution of the long bones. External fixation allows us to maintain bony alignment and length and adequately debride soft tissue areas preparatory to reconstruction of both the bony and soft tissue envelopes. Our goals in these injuries include closure of the wounds with appropriate rotational flaps or grafts or both within the first eight days.

With external fixation in place and frames designed to manage the type of stability needed, we can maintain bony alignment and soft tissue length until wounds are well healed and decide later if we wish to return to the injured area for definitive bone-grafting. Many of these patients have more than one injury and external fixation allows the patient to get out of bed soon, which can improve pulmonary and cardiovascular management and decrease complications in these areas.

If microvascular techniques or local coverage is not possible, external fixation can maintain leg position in cross-leg pedicle flaps—a good alternative to using large plaster casts. Patients are more comfortable and the complete flap can be seen because there are no casts or occlusive dressings in the way.

External fixation is of benefit in extremely unstable comminuted closed fractures and rigidity of the frames can be modified to allow for alignment, but also allow for transmission of forces across the fracture site to stimulate callus formation. Unfortunately, the exact degree of rigidity for ideal periosteal new bone formation is not known and awaits further research.

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Editorials

Medical Associations and the Pace of Change

An increasing pace of technologic and social change is a dominant characteristic of these times. It affects every aspect of society and each is seeking ways to cope. Medical associations are by no means exempt from the stresses this produces and the need to adapt to them. The root cause of all this, of course, is the scientific and technologic progress that is occurring so rapidly in both medicine and society. And the rate of this progress and the pace of this change is not likely to diminish very much in the foreseeable future.

Medical associations are creatures of their member physicians, and must therefore be responsive to their concerns. But they are also human institutions with a life of their own. They each have an internal and an external environment with which they must interact. The internal environment is made up of all the persons who make up the association or who work for it, and their concerns. The external environment is the external world of evolving patient care and social change affecting medicine and its practice, and the public's expectations of the medical profession. The structural organization of medical associations stems from quieter times when the problems of medicine and the society it serves were less complicated and less intertwined with one another. The intrusion, intervention or participation of third parties in medical practice and patient care had not yet occurred to any significant extent and medical associations were able to devote themselves to promoting scientific medicine, professional education and the public health. But now this organizational structure, which worked so well for so long, finds itself hard pressed to cope with the pace of social as well as professional change.

Medical associations are organized as democratic societies governed by their members who individually have a greater or lesser interest in contributing to or participating in this governance. The governance is left to a relative few. Partly for this reason it is the nature of democratic societies to tend to be more sensitive to their internal organizational imperatives than to what may be perceived by many to be the more important imperatives imposed by the external environment. They also tend to be more reactive than proactive. It is often difficult for them to think or plan very far ahead—that is, beyond the next election. It is also in the nature of any association of humans to develop an internal organization or bureaucracy to enable those who work within the association, who are necessarily dependent on one another, to work effectively together. This occurs whether in the federal government, a business corporation or a medical society. Elected or appointed officials become as much a part of these corporate or societal internal organizations as do the hired hands. And, as this internal organization or bureaucracy takes on a life of its own, it develops its own imperatives and also begins to consume organizational resources that tend to be drawn away from the at least equally important organizational goals that are the stated purposes of the organization. To the extent an organization or association becomes absorbed in itself and unduly focused on its internal imperatives, it can lose its ability to effectively pursue the goals in the external environment which are its reason for existence. Since they are always limited, an association's energy and resources must be skillfully deployed if the organization is ever to accomplish its purposes and goals.

It also should be obvious that if an association is to be effective, it is essential that its purposes and goals be clear, within its professional competence to accomplish, and achievable within its resources. One can only wonder how effectively the always limited resources of some of our medical associations are now being used. To what extent are the internal imperatives, important as they always are, drawing energy and resources away from the external imperatives of the association in the world of medical practice and patient care that is changing so rapidly? And to what extent are the external purposes and goals really clearly defined, truly within the competence of the medical profession to accomplish and actually achievable within the resources of the association? One senses that too often medical associations are attempting to achieve goals that are beyond any professional competence they can bring to bear or what resources they have available. Where this is the case it can only amount to an expensive exercise in futility. And one also senses that the natural tendency of any bureaucracy to focus primarily on its internal imperatives may too often be impairing the effectiveness of some medical associations as they attempt to influence the external environment of medical practice and patient care. To the extent any of this is the fact, a review of an association's purposes and specific goals in terms of its internal and external imperatives, and the professional competence and resources it can bring to bear, would seem to be in order. The pace of change in both medicine and society is now so great that the energies and resources of our medical associations must be applied as efficiently and as flexibly as possible to keep up with an ever increasing pace of change, or organizational failure with all of its consequences may be inevitable.

MSMW

Heterogeneity in Type II Diabetes

Rosalyn Yalow and the late Solomon Berson developed the first accurate and reproducible immunoassay for insulin at the Veterans Administration Hospital in the Bronx in the late 1950s.[1] Thus the initial diabetic subjects who were studied had the non-insulin-dependent (type II) or maturity-onset variety of diabetes mellitus, meaning usually normal or high levels of insulin but yet levels that were disproportionately low relative to the concentration of glucose. In the succeeding 2½ decades innumerable papers have appeared discussing this apparent hyperinsulinemia in persons with type II diabetes and Davidson has reviewed many of these studies in this issue of the journal. The observation that increased levels of insulin are required in many middle-aged diabetic persons, however, goes back much further than the early 1960s; soon

after the availability of insulin some 60 years ago, clinicians noted that fat persons with diabetes frequently required relatively large doses of insulin to initiate lowering of glucose values.[2] Likewise, the Scottish pathologist Ogilvie noted that obese persons who did not have diabetes had β-cell hyperplasia at autopsy.[3] In addition, a large number of pathologists dating all the way back to Opie at the turn of the century noted that subjects with diabetes, be they obese or nonobese, showed many degenerative changes in the islets of Langerhans, including fibrosis, glycogen deposition, amyloid infiltration and, in all, a decreased number of β-cells compared with an age-matched population.[4]

Much of the above history has faded into the background by the large amount of research activity in the past decade focused on insulin binding to cells and the decreased binding in insulin-resistant states, as well as the relative role that binding kinetics play in insulin resistance. As reviewed by Davidson, most now feel that the decreased binding is important but less significant than a blunting of insulin's secondary effects inside the cell, which is now the topic of a large number of scientific inquiries around the world. In brief, we really do not yet know how insulin initiates intracellular events. In any case, all of this research and clinical activity has promoted the concept that type II diabetes is due to impedance to the peripheral effects of insulin, in contrast to the earlier literature that primarily indicated decreased β-cell function as the cause. The final answer, as is usually the case in medicine, lies probably somewhere in between. It is best to think of maturity-onset, type II or non-insulin-dependent diabetes mellitus—whichever definition one prefers to use—as a component of a spectrum, ranging on one hand to pure β-cell deficiency and on the other to a severe degree of insulin resistance due to obesity and several other factors. Thus there are some patients, usually in the eighth or ninth decade, who are thin, relatively active and in whom there may be such a degree of β-cell deficiency that they have to be maintained on a regimen of single, and many times twice-a-day, insulin injections. They are essentially as insulin-dependent as would be an adolescent with type I diabetes. On the other end of the spectrum is a person with immense "middle-age spread," weighing 115 to 160 kg (250 to 350 lbs), who has supernormal insulin values, but still not quite enough to overcome the insulin resistance induced by the adiposity, overnutrition and decreased activity. In fact, if one looks at a number of 400 or 500 pounders, a normal glucose tolerance is almost impossible to find other than in some subjects in whom this large degree of obesity was present through childhood and who are then studied in the second or third decade. Thus, theoretically, perhaps even a normal human cannot muster up enough β-cell function should there be a sufficient degree of insulin resistance as in extreme obesity. This is also seen in some of the rare states such as lipoatrophic diabetes in which prodigious insulin secretions can be achieved, but because of the pronounced peripheral insensitivity to the insulin, abnormal glucose homeostasis still ensues.[5]

Finally, why is there clinical heterogeneity in the capacity of β-cells to face the challenge of the insulin resistance associated with obesity, overnutrition and physical inactivity? The guess is that this may be the genetic component, and just as there is heterogeneity in many other inherited traits such as age of menopause or senescence of hair follicles leading to baldness, perhaps there is also an age-related heterogeneous distribution in the normal population in β-cell function, survival and perhaps capacity to divide when the challenge becomes sufficiently great. It is this heterogeneity that is probably inherited and is supported by the fact that identical twins with maturity-onset or type II diabetes are usually 100% concordant, in contrast to the one in two to one in four concordance in identical twins having insulin-dependent or type I diabetes.[6,7]

It has been suggested that many of the other aging phenomena associated with maturity-onset diabetes, including osteoporosis, emphysema, atherosclerosis, cataract and others, might also be related to the earlier β-cell senescence.[8] Perhaps the β-cell is the Achilles' heel, endocrinologically speaking, of the precocious senescence of a number of tissues, and all one needs is the added problem of a little insulin resistance due to one, two or all three of the obesity-overnutrition-decreased physical activity triad.

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Computers and the Physician

THE SLOW but relentless diffusion of computers into the medical workplace and into our medical lives continues to follow a predictable course. Whether we find satisfaction (and see promise) in this, or whether we are repelled by computers and would prefer to ignore them, is pretty well beside the point. Computer programs will find their proper place alongside such former high-technology devices as the clinical thermometer and the hemostat. One question that remains is, when will they find their place in physicians' offices?

Beginning about 30 years ago, the earliest application of computers to medicine took place in research settings where the computational power of the machine could be applied to complex or large-scale mathematical problems of medical significance, or to the storage and management of very large sets of files or records. From the start, there had been these two kinds of applications—arithmetical problems where the computer could perform its logical magic among sets of crisp numbers, and the dull and ponderous shuffling of text passages that it could only push about uncomprehendingly.

When large ("main frame") computers became available to medical investigators during the late 1950s and the 1960s, further applications were envisioned and, among these, the development of large-scale hospital information systems became a sort of holy grail. Launched with much enthusiasm,

projects to develop "total" hospital information systems were established, having the goal of replacing conventional methods of storing, retrieving and communicating medical data and information. Because of this fanfare, the computer (as symbol, not as reality) soon became looked on as a panacea for the annoyances that physicians had long associated with paperwork. The trials encountered in attempting to deliver on these promises have been recounted by several authors.[1,2]

It has now been amply confirmed that medical processes that are intrinsically mathematical in nature and computationally intensive, for example, physiologic monitoring applications, clinical laboratory systems and image processing systems such as the computed tomographic scanner and nuclear magnetic resonance and ultrasound imaging devices, could be profitably dealt with using computers. In contrast, the useful processing of clinical descriptions—the kind of data contained in medical records—has encountered great difficulty. As most physicians realize, the problem is not that ordinary medical text cannot be stored in a computer, but that the computer in its conventional mode of operation cannot "understand" these descriptions. If all that we desire is the passive or inert storage of written descriptions and their subsequent retrieval, computers have long been able to accomplish this. But this offers little beyond what a manila folder or a card file system does and far less than what could be accomplished if the computer could in an interesting way "process" these descriptions. This requires that a computer program can in some sense understand or deal with text, not as a string of meaningless symbols, but as tokens of meaning.

It has been argued elsewhere that what may be called "low-level descriptions"—descriptions consisting primarily of arithmetical or mathematical terms—are far more readily computerized than the "high-level descriptions" that are required with clinical concepts and issues. These are difficult to represent in computer processable form. An analysis based on the structure of medical knowledge suggests that the rapid progress that has been made in developing applications such as billing and accounting systems, and that contrasts so strikingly with the great difficulties (and slow progress) encountered in dealing with medical records, might have been predicted.[3]

In this issue of the journal, Dr Gelman in a Grand Rounds presentation discusses the application of computers in the physician's office setting. This use is in some respects a last frontier of medical computing. After 30 years of computer applications in medical research and nearly 20 years in the development of hospital information systems, attention has become increasingly focused on ambulatory record systems.[4,5] This has happened for institutions of all sizes, but only recently has it been practical to consider the solo practitioner's office as a prospective site.

The opportunities for computers in medical offices have depended on the availability and cost of suitable-sized computer hardware, together with the availability of appropriate application programs. Although a few physicians have learned to program and have written their own office systems, this is not the high road of technology diffusion. The golden age of the automobile began not upon its early introduction, but when the large tool box on the running board, the hand crank, the four or so spare tires and the tire pump could all be dispensed with. So it will be with office computers.

Interestingly, the two extremes of practice scale are probably better served than the middle. For a solo practitioner, in the past two years there has been an emerging of "personal" or small business computers costing on the order of $5,000, which are suitable for many office applications. However, useful software to accompany this hardware is only now beginning to appear, and while there are dozens of office practice packages currently available, most of these are limited to billing and accounting and the most primitive kinds of medical record keeping. More important, most are still relatively untested.

At the other extreme, large-scale ambulatory services have had access to such systems as the well-regarded COSTAR (developed originally at the Massachusetts General Hospital for use for the Harvard Health Plan), which runs on a variety of medium- to large-scale computers. Missing still are systems suitable for intermediate-sized groups where the computing demands are too taxing for single-user personal computers and yet of a scale too small to warrant minicomputer implementations.

Over the past year, a number of medical computing journals and magazines have appeared that are directed to practicing physicians rather than to medical computing specialists. These have addressed in some detail (but with widely varying levels of competence) the practical issues related to computer use in a physician's office. For physicians interested in following developments in this fast moving field, it is likely that these, together with the symposia and tutorials on medical computing being offered by many medical organizations, will satisfy most of their needs.

It is not clear at this point whether physicians need rush to invest in a computer-based office system, and it is surely the case that a great shortage of high-quality *professional* (not merely commercial) software exists.[6] This, however, could change very rapidly and physicians should begin to give closer attention to this field.

It is not too early—nor too late—for those physicians who intend to be practicing for another ten years to begin to acquire what is being called "computer literacy." And it is worth doing this for more reasons than just keeping up with one's own children (or grandchildren)! As prospective users of medical computing systems acquire a modest level of familiarity with computers, they will then be able to evaluate products as they appear in the marketplace, with more confidence and with a far greater likelihood of making wise decisions.

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Do as I Say, or as I Do?

A STUDY by Wells, Lewis and Potter in this issue again calls attention to a relatively low level of concern many physicians appear to have with their own health and a comparable low level of concern of medical societies with the health status of their members. Each physician obviously has his or her own personal attitude toward his or her own health and health maintenance. Presumably these attitudes are not too different from those of the general public except that, because of their professional knowledge and experience, some physicians may be at one extreme—that is, evangelists for every new health measure that comes along—while others at the opposite end of the spectrum of enthusiasm are slower to get on the bandwagon and therefore more nihilistic or fatalistic about health and health maintenance for themselves and others. And some, also like much of the public, are simply afraid and would rather not know if something were wrong with them, and so consciously or unconsciously avoid submitting to health screening or health examinations.

Perhaps it is time, now that more hard data are accumulating, for physicians to begin to practice more of what they as a profession preach. There is reason to believe that when we become convinced of the need and do this, we can be effective. It is generally conceded that members of the medical profession have become convinced and shown the way by sharply curtailing their own cigarette smoking and that this is now having an important effect in the general population. This came about because physicians were so convinced by the data that great numbers of them decided to practice what they had been preaching. "Do as I say" may have had some effect, but "Do as I do" has had much more.

One senses that the time is at hand for physicians to pay more attention to their own health status. In recent years there has been increasing emphasis on the diagnosis and treatment of impaired physicians and this has been a good beginning. But if we expect our patients and the public to be as concerned about their health status as we say they should be, then it behooves us to show them, by the example of what we do, that we are convinced that health assessment and health maintenance are really important and really worth the effort. If health promotion for their physician membership were to become prevalent among medical associations, the members would be well served, and the public could only be impressed and encouraged to do the same thing for themselves.

As discussed in the article "Health Screening of Physicians—A Role for Local Medical Societies," the Fresno-Madera County Medical Society has shown us a way.

MSMW

Case Reports

Spontaneous Colonic Drainage

A Rare Complication of an Amebic Liver Abscess

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LIVER ABSCESS caused by *Entamoeba histolytica*, a protozoan organism, is a common complication of invasive amebiasis in patients seen at Los Angeles County-University of Southern California Medical Center.[1-3] Extension or rupture of an amebic liver abscess into the chest, the pericardium, the peritoneal cavity or the bowel has been reported to occur at a frequency of about 10% with a fatal outcome in 6% to 50% of patients, depending on the organ involved.[4] We describe the history, physical findings and laboratory and roentgenographic features of a successfully treated case of an amebic liver abscess that spontaneously ruptured into the colon.

Report of a Case

The patient, a 30-year-old Honduran man, was in good health until two months before his admission to hospital, when he began to experience right upper quadrant abdominal pain, described as dull and cramping, with intermittent episodes of sharp, severe pain that radiated to his back. The patient had fevers to 38.9°C (102°F), occasional rigors, progressive shortness of breath and weight loss of about 9 kg (20 lb). He said he did not have nausea, vomiting, diarrhea, constipation, hematochezia or hematemesis. He had had no prior surgery and no previous medical problems. He had left Spanish Honduras in 1978 and had worked on a Caribbean cruise ship until settling in Los Angeles in 1980.

On physical examination at the time of admission, he had a pulse rate of 140 per minute, respirations 24, an oral temperature of 38.7°C (101.6°F) and a blood pressure of 140/78 mm of mercury without orthostatic changes. His chest had decreased resonance to percussion over the right lung field from the middle to the base posteriorly with no breath sounds in that area. He had moderate right upper quadrant abdominal tenderness. The liver edge was palpable 2 cm below the right costal margin in the midclavicular line with a span of 18 cm by percussion.

Laboratory values were as follows: hemoglobin, 9.2 grams per dl; leukocyte count, 23,800 per μl with 82% polymorphonuclear cells, 1% bands forms, 10% lymphocytes and 7% monocytes. The proconvertin to prothrombin value was 107%. Serum biochemical test results were as follows: alkaline phosphatase, 321 IU per liter (normal 60 to 110); albumin, 2.5 grams per dl (normal 3.9 to 5.0), and alanine aminotransferase, 66, and aspartate aminotransferase, 39 IU per liter (normal 5 to 40). A chest roentgenogram showed an elevated right hemidiaphragm to the fourth rib posteriorly with some atelectasis (Figure 1). A real-time ultrasound examination showed a 14-cm hypoechoic area in the right lobe of the liver consistent with an amebic abscess. (The patient had no stool to examine on admission.)

Hospital Course

The patient was treated with chloroquine phosphate given orally, based on a presumptive diagnosis of an amebic liver abscess. On the second hospital day, he had a temperature of 38.6°C (101.5°F) with right upper quadrant abdominal pain and tenderness that subsided after one episode of diarrhea. The diarrheal specimen was reddish brown and laboratory studies showed it to be positive for polymorphonuclear leukocytes and trophozoites of *E histolytica*. A repeat chest roentgenogram and an upright abdominal roentgenogram immediately after the diarrhea showed air within the liver (Figure 2). The chloroquine therapy was discontinued and a regimen of metronidazole given orally was begun. A repeat

Figure 1.—An upright chest roentgenogram taken on admission.

(Armen RC, Fry M, Heseltine PNR: Spontaneous colonic drainage—A rare complication of an amebic liver abscess. West J Med 1985 Feb; 142:253-255)

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ultrasound examination the next day showed the liver to contain air within the hypoechoic area that now measured about 11 cm in diameter. A computed tomographic scan of the abdomen showed air in the liver abscess cavity and an adhesion of the hepatic flexure of the colon to the liver. No hepatocolic fistula was found by barium enema study. The amebic hemagglutination titer was reported as 1:2,000. The patient was treated with oral metronidazole for a total of 21 days with no subsequent episodes of diarrhea or fever. On follow-up examination two months later the patient had no abdominal pain, no fever or chills and no diarrhea. The liver edge was at the right costal margin in the midclavicular line and the leukocyte count and blood chemistries were at normal levels. A repeat chest roentgenogram showed no elevation of the right hemidiaphragm and no air in the liver.

Discussion

This case shows a characteristic presentation of an amebic liver abscess with the unusual outcome of presumed spontaneous rupture and drainage of the material from the abscess cavity into the colon. The precise incidence of amebic liver abscess in the United States is unknown. Liver abscess is the most commonly recognized complication of invasive amebiasis. When an amebic liver abscess ruptures, it is usually through the diaphragm into the right chest. This has been reported in 7% to 20% of published cases.[4-6] An amebic liver abscess may also rupture into adjacent structures such as the peritoneal cavity, the pericardium, the biliary system and the kidney, but rupture into the bowel has rarely been documented. In his book, Craig compiled the early published reports on the location of rupture of amebic liver abscesses. Of 624 cases of liver abscess, 192 ruptured, but only 6 into the colon.[5] More recently, a fistula between an amebic liver abscess and the colon was shown directly in one patient. This liver abscess cavity, when aspirated, showed not only "anchovy paste" but pus that smelled foul. When cultured, the pus grew two different types of bacteria.[7] In the study of Adams and MacLeod from South Africa, 215 of 2,074 patients had amebic liver abscesses that ruptured.[4] In only three of these patients, however, did the abscess rupture into the bowel and two of the patients died. The abscess rupture of one of the patients was identified in the same manner as in our patient: amebic pus was passed rectally. The frequency with which an abscess is resolved in this way may be underestimated because the material from an amebic liver abscess cavity via the gastrointestinal tract may pass unnoticed in a severely ill patient.

Chloroquine, because of its tissue amebicidal activity, was used initially in our patient as a therapeutic trial to differentiate between an amebic or a pyogenic liver abscess.[3,4,8] Metronidazole therapy was begun after the diagnosis of ruptured amebic liver abscess was made because it is the drug of choice.

Although we did not show a direct connection between the liver abscess cavity and the colon, the finding of air within the liver immediately after the episode of diarrhea and the close

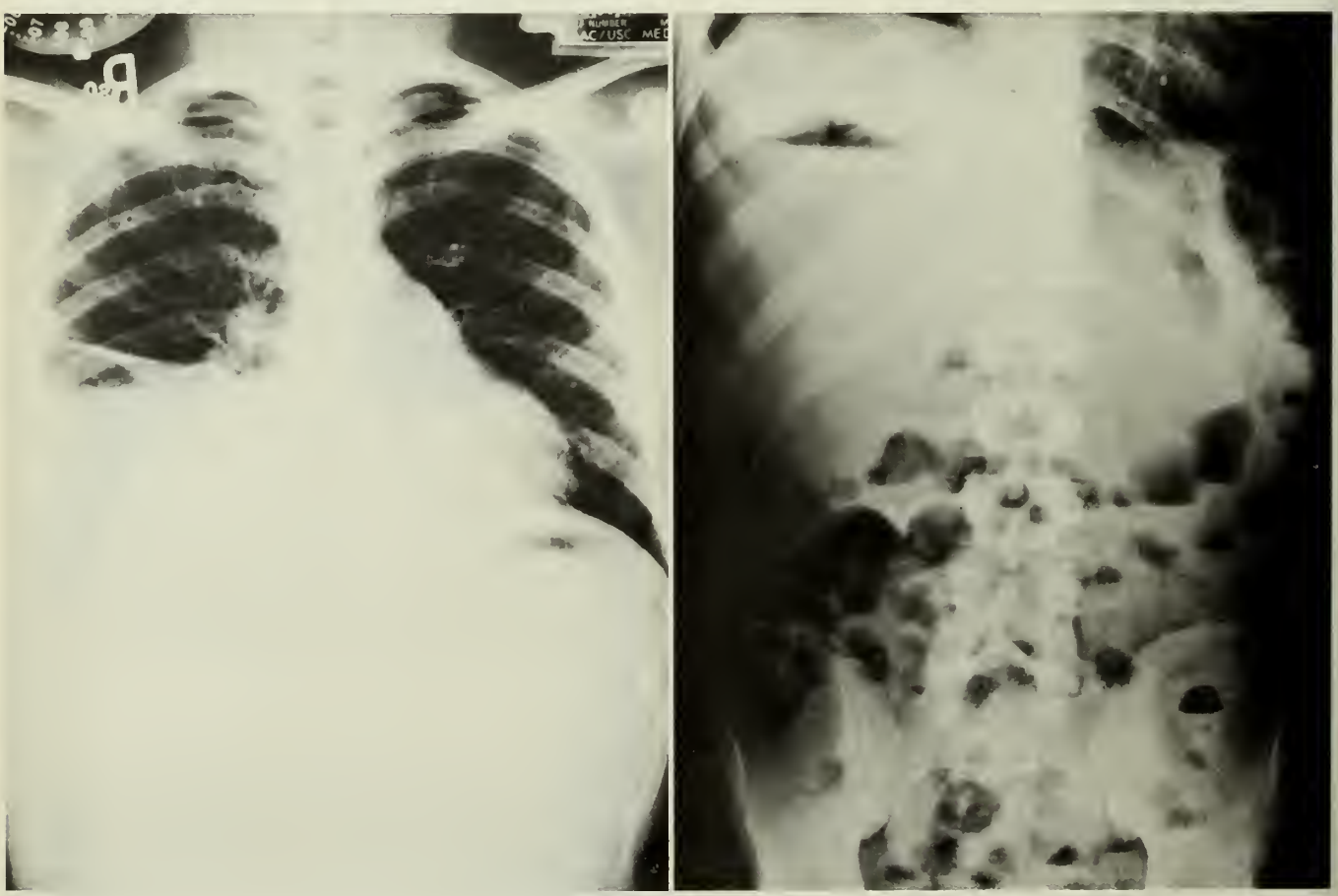

Figure 2.—Left, An upright chest roentgenogram taken immediately after the episode of diarrhea. **Right,** Another upright chest roentgenogram taken immediately after the episode of diarrhea.

proximity of the hepatic flexure of the colon to the liver strongly suggest that decompression occurred through the colon. The otherwise uncomplicated recovery of this patient shows the possibly benign natural course of an amebic liver abscess that drains into the colon.

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Neisseria sicca Endocarditis in Intravenous Drug Abusers

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Neisseria sicca is one of many species of *Neisseria* that are normal inhabitants of the nasopharynx. This organism has generally been considered nonpathogenic. Since 1918 there have been seven cases of *N sicca* endocarditis reported in the literature.[1] We now report two additional cases in intravenous drug abusers.

Reports of Cases

Case 1

The patient, a 41-year-old man with a history of intravenous abuse of codeine and methylphenidate hydrochloride, was admitted to Los Angeles County-University of Southern California (LAC-USC) Medical Center because of malaise, fever and chills starting four days before admission. He had sporadically taken erythromycin and tetracycline orally for exhaustion. On physical examination at admission, he had an oral temperature of 40.5°C (104.9°F), many dental caries and a grade 1/6 systolic ejection murmur, best heard along the left sternal border. His peripheral leukocyte count was 15,600 per μl, with 80% polymorphonuclear leukocytes and 4% band cells. A chest radiograph showed infiltrates in the left midlung and right lower lung fields, consistent with embolization. Infective endocarditis was suspected. Blood specimens were drawn for culture and the patient was given vancomycin hydrochloride intravenously (he had a history of penicillin allergy) and gentamicin sulfate. Six days later, one of five of the blood specimens cultured yielded Gram-negative cocci, later identified as *N sicca*. The patient's fever resolved, but on the seventh hospital day the central venous catheter was accidentally disconnected. Because all but one blood culture were negative for the pathogen, it was decided not to reinstate the intravenous line; instead, the patient was given erythromycin by mouth. Fever of 40.5°C (104.9°F) subsequently developed. Treatment with vancomycin and gentamicin was begun again, but high fever continued. On the ninth day in hospital, his treatment was changed to intravenous administration of cefazolin sodium, resulting in defervescence after two days.

On the 13th day the patient was transferred to Rancho Los Amigos Hospital (Downey, Calif) for continuation of antibiotic therapy for a presumptive culture-negative infective endocarditis. The antibiotic regimen was discontinued for two days to determine the true nature of his bacteremia. Within 24 hours his temperature rose to 41.6°C (107°F). He was consequently treated again with vancomycin and gentamicin. Six of seven sets of cultures of blood specimens obtained during the time when the patient was not receiving antibiotics yielded *N sicca* sensitive to penicillin. The patient left the hospital against medical advice before therapy was completed.

Case 2

The patient, a 24-year-old man with a history of intravenous cocaine and heroin abuse, was admitted to LAC/USC Medical Center after experiencing fever, chills, malaise, right pleuritic pain and transient hemoptysis for ten days. The fever and chills had persisted despite one week of self-treatment with penicillin taken orally and ampicillin. He had had no previous cardiac disease or heart murmurs. On admission the patient had a temperature of 40°C (104°F) accompanied by shaking chills. Physical examination was remarkable for a grade 3/6 early systolic murmur at the left midsternal border, which was accentuated by inspiration or squatting. He had a leukocyte count of 9,500 per μl with 84% polymorphonuclear leukocytes and 3% band cells. A chest radiograph showed nodular infiltrates in the right lower lobe. The patient was given oxacillin sodium intravenously and tobramycin for a tentative diagnosis of bacterial endocarditis with multiple septic pulmonary emboli. Six out of six blood cultures from specimens taken on admission yielded oxacillin-sensitive *Staphylococcus aureus*. Treatment with tobramycin was discontinued. An echocardiogram showed a "pea-sized" tricuspid vegetation. The patient's fever subsided and serial chest films showed gradual resolution of the infiltrates. After ten days of oxacillin therapy, the patient left the hospital against medical advice.

He returned to the medical center 12 days after his initial admission with a temperature of 40°C (104°F), shaking chills and an unchanged heart murmur. The patient was given oxacillin intravenously after three specimens of blood for culture were drawn. The blood cultures yielded no growth.

The patient was transferred to Rancho Los Amigos Hospital 17 days after his readmission to complete a four-week course of parenteral antibiotic therapy. He was treated with nafcillin sodium given intravenously. One day after comple-

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tion of his four-week course of antibiotic therapy, fever to 39°C (102.2°F) ensued. Nafcillin therapy was restarted after blood was drawn for culture. His therapy was changed to intravenous administration of ampicillin when ampicillin-sensitive *N sicca* was isolated from six of eight sets of blood cultures. The patient responded well to ampicillin therapy and his fever dropped for several days, after which left pleuritic pain and low-grade fever developed. A chest roentgenogram and ventilation-perfusion scan were suggestive of new pulmonary emboli at the left lower lobe; these gradually resolved in a week. Ampicillin therapy was discontinued after completion of a four-week course. The patient remained afebrile for ten days, at which time fever and shaking chills recurred. Ampicillin-sensitive *N sicca* was once again isolated from three of four sets of blood cultures. Removal of the tricuspid valve was contemplated and the patient was transferred to Harbor-UCLA Medical Center (Torrance, Calif).

At Harbor-UCLA Medical Center, the patient was given penicillin and gentamicin, but fever persisted and bilateral lower lobe infiltrates developed. Oxacillin was added to the regimen of penicillin and gentamicin. The patient's fever gradually resolved and he completed four weeks of therapy with these antibiotics. Blood cultures yielded no growth after the antibiotic regimen was discontinued and the patient remained afebrile until discharge to home.

Microbiology

Blood specimens for culture were collected in 90-ml bottles of trypticase soy broth and Schaedler's medium, each containing 0.03% sodium polyanethol-sulfonate and 6% carbon dioxide (BBL, Cockeysville, Md). The trypticase soy broth was vented before incubation of the cultures. The organisms were positive for oxidase and showed acid reaction in cysteine trypticase agar for glucose, maltose, fructose and sucrose but not lactose. Microtube-dilution susceptibility testing[3] showed that both organisms were susceptible to penicillin, ampicillin, chloramphenicol, tetracycline, methicillin and gentamicin. Macrotube-dilution susceptibility testing for ampicillin and gentamicin showed minimal inhibitory concentrations of 0.4 and 0.8 μg per ml for the isolate from patient 1 and 0.2 and 0.02 μg per ml for isolate from patient 2. Minimal bactericidal concentrations for ampicillin and gentamicin were 0.4 and 0.8 μg per ml for the first patient and 0.4 and 0.05 μg per ml for the second. A synergistic isobologram study for ampicillin and gentamicin was done on isolate No. 2 and showed antagonism between the two drugs (Figure 1). A test for β-lactamase production on this same isolate, using the chromogenic cephalosporin (Cefinase, BBL) disc method yielded a negative result. Serum bactericidal activity in patient 2 occurred at a 1:32 dilution.

Discussion

Patients with *N sicca* endocarditis in cases reported in the literature presented with symptoms similar to those seen in these two men. They had fever with temperatures as high as 39°C (102°F) or more, sudden onset of symptoms, multiple embolic phenomena and delayed arrival at the diagnosis. Mortality was extremely high in the preantibiotic era.[1] The first successfully treated case was reported in 1941 when the patient described received three weeks of heparin and sulfapyridine therapy.[2] The remaining patients were treated with either sulfapyridine or penicillin with or without streptomycin. The organisms found in the cases presented here were quite sensitive to penicillin and ampicillin.

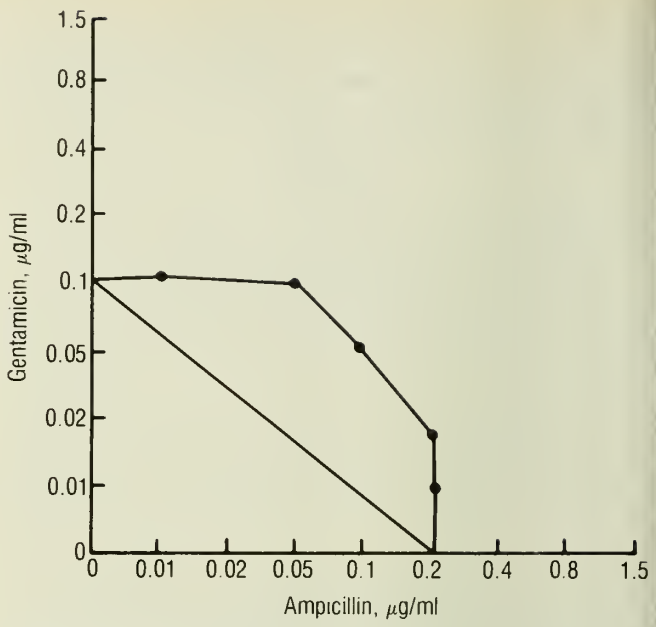

Figure 1.—Isobologram of the minimal inhibitory concentrations of ampicillin and gentamicin for isolate No. 2.

The reason for the repeated medical failures in case 2 is unclear. Some possibilities should be considered: (1) inadequate response to ampicillin when used alone (in vitro studies, however, showed antagonism between ampicillin and gentamicin), (2) β-lactamase production that was neutralized by oxacillin, allowing ampicillin to work more effectively (however, this organism was β-lactamase-negative), (3) *S aureus* was not eradicated by previous therapy.

It is not clear why *N sicca* endocarditis develops in some persons. Poor dental hygiene and practices of licking and sharing of needles may be factors that predispose these patients to infection with bacteria from oral flora. It is difficult to say whether the fact that both of these patients were taking oral antibiotics while continuing to use drugs intravenously played any role in the development of their infection. The oral antibiotics may have suppressed the more exquisitely antibiotic-susceptible component of the oral flora, allowing the more resistant *N sicca* to become predominant and increasing their suceptibility to be infected by this "nonpathogenic" organism. *N sicca* should not be readily dismissed as a blood culture contaminant, especially in the setting of parenteral drug abuse, and should be added to the list of microorganisms responsible for infective endocarditis in intravenous drug abusers.

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An Unusual Systemic Staphylococcal Illness With Features of the Mucocutaneous Lymph Node Syndrome

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STAPHYLOCOCCI PRODUCE several distinct but related diseases, including the scalded skin syndrome, bullous impetigo, a scarlet fever-like illness and the staphylococcal toxic shock syndrome. These individual staphylococcal syndromes share many features in common. Often the assignment of a definitive diagnosis to a specific staphylococcal illness is complicated by the multiplicity of separate syndromes, the relative paucity of diagnostic criteria and the absence of definitive laboratory tests.[1]

The mucocutaneous lymph node syndrome is a disease of unknown cause that shows many of the characteristics of a staphylococcal toxin-mediated systemic disease.[2] Epidemiologic, immunologic and clinical features support the existence of an infectious agent in the early stages of the illness.[3,4] The mucocutaneous lymph node syndrome has a pronounced predilection for the younger pediatric population, which is emphasized by the rare occurrence of any similar disease in older persons.[5] Arguably, the mucocutaneous lymph node syndrome is a disease only of children, and similar illnesses in adults are by definition variants of other staphylococci-mediated processes. The report of the occurrence in an adult of an unusual systemic disease with features of this syndrome, as well as of staphylococcal toxic shock syndrome and staphylococcal scarlet fever, underscores the diagnostic dilemmas imposed by the protean clinical presentation of the systemic staphylococcal syndromes, and affords insights into the possible cause of the mucocutaneous lymph node syndrome.

Report of a Case

The patient, a 35-year-old woman previously in good health, was transferred from another hospital to the University of Utah Medical Center with an illness characterized by 15 days of fever, progressive malaise, arthralgias and myalgias. At the time her illness began, the patient was a vigorous, athletic mother of one who was not menstruating, did not use tampons and who had no known environmental exposures resulting in her symptoms.

Ten days before the onset of the illness, the patient noted painful erythematous vesicles over the pretibial regions. These lesions resolved spontaneously over four to five days. Subsequently a nonpruritic, reticular rash developed on the right thigh. A few days later the patient had fatigue, fever, chilling with rigors, headaches, myalgias, right knee pain and bilateral axillary pain. She was admitted to hospital at another institution.

In Figure 1 is summarized the clinical course of the first and second hospital admissions. On initial evaluation the patient appeared ill and had a blood pressure of 115/70 mm of mercury and a temperature of 38°C (100.4°F). The leukocyte count was 16,700 per μl with 50% bands, 47% segmented cells, 2% lymphocytes and 1% monocytes. The hematocrit was 37% and the platelet count normal. A Westergren sedimentation rate was 40 mm per hour. A specimen of clean, voided urine contained 1+ protein, 3+ hemoglobin, two to four erythrocytes, three to five leukocytes and one to three epithelial cells per high-power field and a few bacteria. Rheumatoid factor, Monospot slide test for infectious mononucleosis, antistreptolysin 0 titers and febrile agglutinins were negative. An electrocardiogram (ECG) showed minor nonspecific ST-T abnormalities. Culture of specimens from the throat and vagina grew normal flora without staphylococci or pathogenic streptococci. Blood cultures were negative.

The patient was treated with a regimen of indomethacin without improvement. On the second hospital day the temperature by mouth was 39°C (102.2°F). A sore throat, red tongue and ulcerations of the buccal mucosa were noted. An antinuclear antibody titer of 1:640 was reported, a diagnosis of systemic lupus erythematosus was made and therapy with prednisone, 60 mg a day, was instituted. Headaches, myalgias and arthralgias continued and the patient was transferred to the University of Utah Medical Center on the 15th day of her illness.

On admission to the medical center, the patient was lethargic, irritable and complained of muscle pain with slight movements. Her temperature was 36.8°C (98.2°F), pulse 72 beats per minute and blood pressure 130/78 mm of mercury. Photophobia was noted. A prominent diffuse morbilliform rash was apparent on the face, trunk and hands. Erythematous blanching papules were present over the anterior and lateral surfaces of the lower extremities. The oropharynx was erythematous with a small, well-demarcated shallow ulceration on the right tonsillar pillar. The lips and tongue were red and dry. No cervical adenopathy was present, but there was bilateral axillary adenopathy with a tender 3 cm left axillary lymph node. Cardiac examination showed no abnormalities. There were effusions in the knees, ankles and proximal interphalangeal joints and mild swelling of the upper and lower extremities. On musculoskeletal examination she had diffuse weakness due to pain. There were no focal neurologic findings.

A leukocyte count was 16,000 per μl with 84% segmented cells, 2% bands, 1% eosinophils, 11% lymphocytes and 2% monocytes. The hematocrit was 39.1% and the platelet count slightly elevated at 419,000 per μl. The Westergren sedimentation rate was 79 mm per hour. A urine specimen contained an occasional leukocyte and a few bacteria. The serum albumin level was 3.5 mg per dl, and the serum liver and muscle enzymes, blood urea nitrogen and creatinine were within normal limits. The cerebrospinal fluid contained no cells and

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had a protein of 20 mg per dl. Serologic studies were negative for cytomegalovirus, rubella, rheumatoid arthritis, syphilis, hepatitis B surface antigen and mononucleosis. An antinuclear antibody titer was 1:20. A lupus erythematosus preparation and anti-double-stranded DNA antibody were negative. Complement fixing antibodies to blastomycosis, coccidioidomycosis and histoplasmosis were also negative, as were agglutinating antibodies to *Proteus* OX-2, OX-K and OX-19; *Salmonella* A, B, C, D and E; typhoid O and H; paratyphoid A, B and C, and *Brucella* antigens. Titers for *Mycoplasma*, adenoviruses A and B and *Chlamydia* were not elevated. Serum complement levels were C3, 167 mg per dl; C4, 41 mg per dl, and C3 proactivator (C3PA), 63 mg per dl. The C3 and C3PA were mildly elevated. Results of an ECG were normal. Intradermal delayed hypersensitivity testing for *Candida*, coccidioidomycosis and mycobacteria was negative. Cultures of specimens of blood, cerebrospinal fluid and urine on standard bacterial and fungal media were negative.

The prednisone regimen was discontinued at the time of admission. Over the next day the patient had increasing headaches, myalgias and pharyngitis. Treatment with indomethacin (Indocin) was reinstituted without effect. On the 16th day bilateral, nonexudative, sterile conjunctivitis and lip fissures were noted for the first time. New 1- to 2-mm erythematous papules appeared on the extremities.

Skin biopsy specimens of a new leg lesion showed a superficial lymphohistiocytic infiltrate that was predominantly lichenoid with some perivascular component. There was vacuolar degeneration of basal cells with individually necrotic keratinocytes but no vesicles were seen. Direct immunofluorescence of biopsy specimens obtained from both involved and sun-exposed, uninvolved skin failed to show any evidence of deposition of IgG, IgM, IgA or C3 at the dermal epidermal junctions or around superficial dermal blood vessels. On the basis of this negative "lupus band test" a diagnosis of lupus erythematosus was considered unlikely.

On the 17th day, the patient had pronounced increase in her malaise, myalgias and headaches. A temperature taken orally was 36.6°C (98.0°F) and blood pressure was 138/68 mm of mercury. Despite being afebrile, the patient was immobilized by muscle pain, resisted any movement and was unable to care for herself. Aspiration of the left axillary lymph node, initially thought to be reactive, produced 8 ml of purulent-appearing material that contained many polymorphonuclear leukocytes and Gram-positive cocci in clusters. Treatment with nafcillin sodium, 1 gram every four hours, was started and the indomethacin therapy was discontinued. Culture of the aspirated material subsequently grew *Staphylococcus aureus* sensitive to the penicillinase-resistant penicillins. Total leukocyte count at that time was 18,200 per μl with 12% bands, 66% segmented cells, 1% eosinophil, 1% basophil, 9% lymphocytes and 11% monocytes.

On the 18th day the patient continued to have generalized complaints but remained afebrile. Increased palmar erythema and phalangeal edema were noted, which were accompanied by periungual desquamation of the right index finger. The left axillary adenitis increased despite antibiotic therapy and was surgically incised and drained. An indium In 111 leukocyte scan showed accumulation only in the area of the left axillary node. An echocardiogram showed no valvular or coronary artery abnormalities.

Over the next two days the patient's condition improved. The conjunctival redness, lip fissures and adenitis decreased and the lower extremity lesions resolved. The patient's physical activity and sense of well-being increased dramatically, and she was discharged with a ten-day course of dicloxacillin

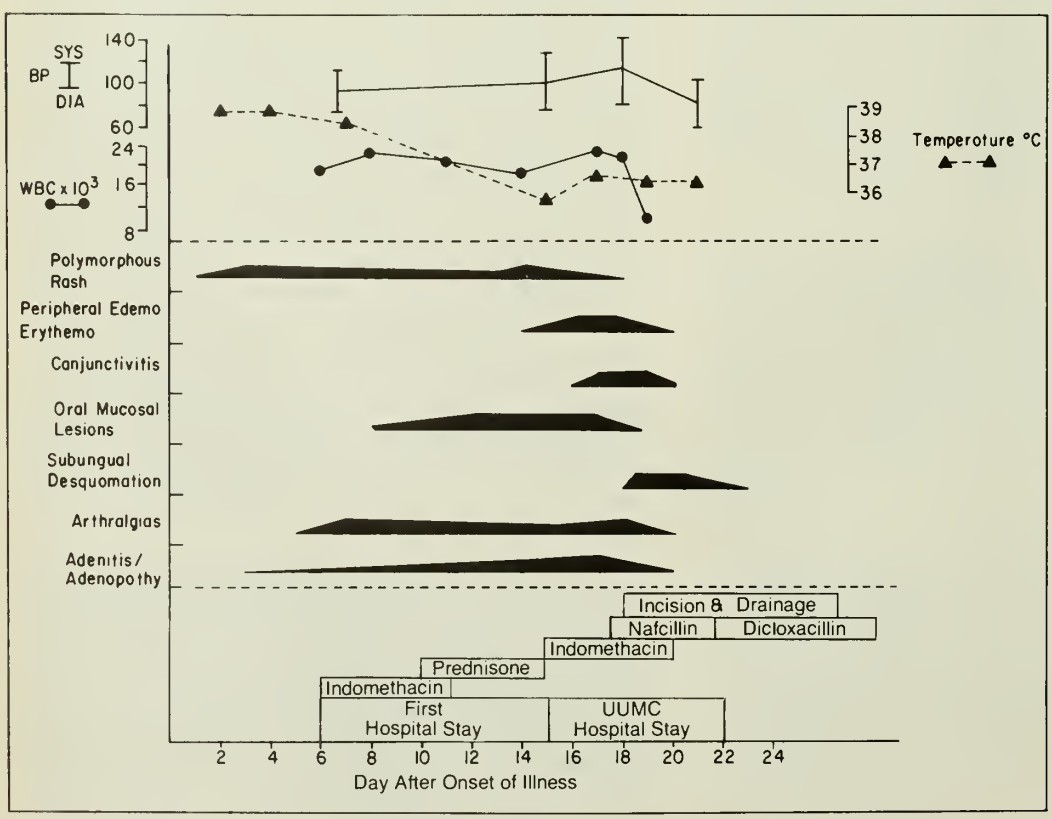

Figure 1.—Clinical course during both hospital admissions. UUMC = University of Utah Medical Center.

sodium on the 22nd day after the onset of her illness. Before discharge the leukocyte count was 8,200 per μl with a normal differential. A Westergren sedimentation rate was 54 mm per hour and an ECG was normal.

Three weeks following discharge she was still fatigued but otherwise symptom-free.

Discussion

This case presents many of the diagnostic and laboratory findings of the mucocutaneous lymph node syndrome.[6] The syndrome is defined by the presence of fever of more than five days' duration, conjunctival injection, oral mucosal changes, induration of the hands and feet, palmar and plantar erythema, periungual desquamation beginning about two weeks after onset of the illness, diffuse erythematous rash and enlarged lymph nodes with at least one node 1.5 cm or larger in diameter.[4,5] The absence of nonsuppurative cervical adenopathy, the presence of staphylococcal axillary adenitis and the age of our patient did not fit the case definition of the mucocutaneous lymph node syndrome.

The patient was showing an advanced degree of morbidity at the time a percutaneous needle aspiration disclosed the presence of a staphylococcal infection. Nevertheless, prompt resolution of constitutional symptoms followed surgical drainage of the affected lymph node and the systemic administration of antistaphylococcal antibiotics. Failure to alter the course of the disease process with antibiotics alone is similar to observations of the lack of utility of appropriately administered antistaphylococcal drugs in cases of the mucocutaneous lymph node syndrome in children with pronounced cervical adenopathy[7] and shows that a failure to respond to antibiotics does not exclude an infectious cause for this or other toxic syndromes.

Identification of a staphylococcal origin of our patient's illness encourages attempts to classify it as one of the existing, recognized toxic syndromes of staphylococcal origin such as a highly atypical variant of the more commonly recognized nonmenstrual staphylococcal toxic shock syndrome.[8,9] Such a diagnosis is supported by the patient's age and sex, a coexisting staphylococcal infection and the multisystem involvement.[10] However, the nature of the multisystem disease mitigates against this diagnosis. In particular, the lack of hypotension, thrombocytopenia, myositis or nephritis makes this diagnosis questionable. It is possible that intermittent therapy with steroids given orally and nonsteroidal anti-inflammatory agents may have altered this patient's clinical course, confusing the diagnosis. Alternatively, the patient's unusual syndrome may be another example of the staphylococcal scarlet fever syndrome. The severe degree of morbidity, lack of scarlatiniform rash and the absence of characteristic dermatopathologic changes consisting of intraepidermal cleavage through desmosomes of the stratum granulosum[11] make this diagnosis unlikely as well.

The exact designation of our patient's staphylococcal syndrome remains unresolved. Cases have been reported previously of adults who had the mucocutaneous lymph node syndrome[12-14] and scarlet fever-like illnesses.[15] Most of these cases involved young women, some of whom were menstruating or had documented staphylococcal infections with significant systemic toxicity. In retrospect, these cases were probably of the staphylococcal toxic shock syndrome.[16] The scalded skin syndrome in children is also occasionally misdiagnosed as the mucocutaneous lymph node syndrome. The pronounced similarity in these syndromes and perhaps their variants are responsible for the difficulty in achieving a diagnosis. Whether a separate syndrome or a variant of the strictly defined mucocutaneous lymph node syndrome, staphylococcal toxic shock syndrome or staphylococcal scarlet fever, the current case has the potential for increasing the understanding of the cause of serious and at times fatal diseases of children and adults.

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Correspondence

The Editorial Board will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words, and must be typewritten, double-spaced and submitted in duplicate (the original typescript and one copy). Authors will be given an opportunity to review any substantial editing or abridgement before publication.

Thyrotoxic Periodic Paralysis in Navajos—HLA Typing

TO THE EDITOR: Periodic paralysis is a well-recognized complication of hyperthyroidism.[1-4] Although it occurs not infrequently among Chinese[1] and Japanese[2] men with thyrotoxicosis, it is rare among other ethnic groups.

Report of a Case

An 18-year-old Navajo man* presented to the emergency room complaining of paralysis of all extremities. He had had a tremor of the hands for two years before this admission and also admitted to insomnia and anxiousness. Beginning three nights before admission and recurring each night, he noted weakness of all extremities lasting until the following morning when it resolved spontaneously. On the morning of admission, however, it failed to resolve. He found himself unable to sit up or walk, and so was brought to the emergency room. There was no association of the symptoms with preceding heavy carbohydrate intake or exercise. He denied any family history of similar episodes.

On physical examination the patient appeared anxious. His pulse was 104, bounding peripherally, and blood pressure 120/52 mm of mercury. The thyroid was slightly enlarged and smooth. Power of the extremities ranged from 2− to 3/5 in all extremities with greater loss of power in the lower extremities, the left side and the proximal muscle groups. Despite this, reflexes were 2+ and symmetric. In addition, the cranial nerves were intact bilaterally, sensory and cerebellar functions were preserved and Babinski's signs were plantar. A fine tremor was also noted.

Initial laboratory values included the following: potassium 2.0 mEq per liter, carbon dioxide 14.7 mEq per liter and creatine kinase 2,256 units per liter, while an electrocardiogram showed U waves and sinus tachycardia. Sodium, chloride, complete blood count, glucose, urinalysis, blood lead concentration, serology and drug screen were all within normal limits. The patient was initially managed with potassium supplementation with return of full function (although some aching in the legs persisted). The patient was then begun on a regimen of propranolol hydrochloride for the clinical thyrotoxicosis. When a total thyroxine level drawn on admission was reported as 17.6 mEq per dl (normal 5 to 12), he was begun on a regimen of propylthiouracil. For the remainder of his hospital stay, he had no repeat episodes of either hypokalemia or muscle weakness.

At follow-up three weeks later, he recounted a single episode in the interim of slight weakness following heavy exercise. Findings on examination were normal, and the same medications were continued. After then being lost to follow-up for three months, he returned complaining of increasing episodes of bilateral leg weakness especially after exercise. He also had increased symptoms of thyrotoxicosis. Examination showed signs of thyrotoxicosis (tachycardia, diaphoresis, tremor, thyroid enlargement, lid lag and mild exophthalmos). Neurologic examination showed no abnormalities. Laboratory values included serum potassium of 2.7 mEq per liter, total thyroxine of 29.3 μg per dl, and a free thyroxine index of 16.6 (normal 1.6 to 5.6). Administration of the medications was restarted. Once more, he was lost to follow-up for four months. On return, he had recurrent signs of thyrotoxicosis but no paresis. Serum thyroxine and free thyroxine index values were elevated. Because of compliance problems, he subsequently underwent radioiodine therapy and after six months has had no recurrence of symptoms.

HLA (human leukocyte antigen) typing on the patient showed the following antigens: A2, A−, Bw62, Bw39, Cw1, Cw− and supertype Bw6.

Discussion

Another case was previously reported by Conway and co-workers[5] and is included to report the results of HLA typing. Briefly, the patient, a Navajo man, was 31 years old when he first began experiencing infrequent periodic paralysis after heavy carbohydrate ingestion. Somewhat later thyrotoxicosis developed, and he was treated with iodine 131. Twelve years later he has had no recurrences of the hyperthyroidism or periodic paralysis.

HLA typing was done on the patient and showed the following antigens: A2, Aw31, Bw39, Bw62, Cw1, Cw− and supertype Bw6.

There are no known relations between the two patients.

Periodic paralysis has been reported as a complication of hyperthyroidism since 1902.[4] The vast majority of cases in the literature have been in patients of Chinese[1,6] or Japanese[2,4] ancestry. Among these groups, thyrotoxic periodic paralysis (TPP) has been found to occur in 8.25% to 19.2% of men and 0.2% to 0.4% of women with hyperthyroidism.[1,2,7] A male-to-female ratio of these patients with hyperthyroidism who have TPP is given as 6 to 20:1,[2,4] despite the fact that the male-to-female ratio of patients with only thyrotoxicosis is 1:7.[8]

*Dr Bruce Tempest provided assistance with this case.

The opinions expressed in this paper are those of the author and do not necessarily reflect the views of the Indian Health Service.

TPP is a much rarer condition among patients of other ethnic ancestries, but does occur. Conway and associates,[5] in their report of four cases, including two Pueblo Indians and the only other Navajo reported with TPP, commented on the lack of reports of American Indians with TPP. They noted the anthropologic evidence favoring an Asian origin of the American Indians, evidence that might suggest that TPP would be seen more commonly in this group. However, if one considers the population figures, the prevalence may not be as low as would appear. The 1983 population of Navajos on or about the reservation is 161,352. If the estimate of prevalence of Graves' disease in the United States of 0.4%[9] holds true among the Navajo, there should be a prevalence of 645 cases; with a male-to-female ratio of 1:7, about 80 cases will be in men. The two reported cases alone constitute a 2.5% prevalence rate of TPP among thyrotoxic Navajo men, by this calculation.

In 1978 Yeo and co-workers [6] reported the first examination of HLA typing of patients with TPP. They found in 21 Chinese men with TPP, and in 26 with Graves' disease but not TPP, a significantly increased frequency of Bw46/B40 over controls. Of more interest, they found in TPP patients a linkage disequilibrium with A2/Bw22 of a statistically significantly increased frequency, and with Aw19/B17 that just failed to achieve statistically significantly increased frequency over non-TPP patients and controls. Guan and Cheah[7] reported that their patient also had A2/Bw22 type. These two patients, therefore, differ from those previously reported in their HLA typing. In addition, they have none of the patterns of linkage disequilibrium previously reported to occur among Navajos.[10] The significance of the shared antigens of these patients and of the difference from those previously reported must await further reports.

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Exercise for Patients With Neuromuscular Diseases

To the Editor: Despite many commendable points, "Prescribing Exercise" by Drs Goldberg and Elliot[1] in the September issue disappoints by neglecting a large group of patients with neuromuscular disorders. Their brief early reference to "musculoskeletal problems . . . altering the type of activity prescribed" is not sufficient to counteract the inclusion of such disorders and "chronic illness" in the list of relative contraindications to exercise later in the article.

It is true that most physicians until the 1950s (and some even today) regarded active exercise as positively harmful in many neuromuscular diseases, particularly muscular dystrophy (MD) and amyotrophic lateral sclerosis (ALS). Meanwhile, many injured athletes provided practical demonstrations of the value of graded exercise during convalescence from acute injuries, and it became appreciated that the addition of disuse atrophy to preexisting weakness due, for example, to MD or ALS, increased a patient's disability.[2] There can now be little doubt that active exercise programs benefit patients suffering from such apparently hopeless diseases as MD[2-4] and ALS.[5,6] The question has become not *whether* to prescribe exercise but *how much* of *what kind*. Everyone is susceptible to the disuse syndrome.[7]

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A Preventable Endemic Condition

To the Editor: The excellent December edition of *The Western Journal of Medicine* devoted to Personal Health Maintenance highlighted many areas in which preventive medicine could possibly reduce mortality. For most of these conditions, the anticipated benefits of even the most efficacious and widely applied measures will accrue to only a small proportion of those at risk. It was disappointing to find, even among expositions of societal influences and environmental risk factors, no mention of a preventable endemic condition claiming the lives of more than 20,000 Americans each year. This condition has a per capita death rate about 100 times higher in the United States than in comparable western countries. Eradication of the causative agent by the methods so demonstrably effective in these countries would presumably eventually reduce death rates to similarly low figures in the United States.

The condition is, of course, death from the unrestrained availability of hand guns. Clearly this falls within the province of preventive medicine.

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Hyperkalemia—Consider the Possibility of a Pseudoabnormality

TO THE EDITOR: We enjoyed the recent medical staff conference on hyperkalemia, but wish to remind readers to consider the possibility of pseudohyperkalemia in the differential diagnosis of the etiology of this condition.[1] Pseudohyperkalemia associated with thrombocytosis is a well-described abnormality which may occur in chronic granulocytic leukemia, polycythemia rubra vera, agnogenic myeloid metaplasia or primary thrombocytosis.[2] In these cases the platelet count is usually greater than $1,000 \times 10^9$ per liter. The artifact in these conditions appears to involve the release of platelet potassium during coagulation and diagnosis of pseudohyperkalemia can be readily confirmed by determining a plasma potassium level. Recently in a patient with chronic granulocytic leukemia with thrombocytosis a normal electrocardiogram in the face of a serum potassium of 7 mmol per liter was a clue to the existence of pseudohyperkalemia.

In their review, Alvo and Warnock recommended instituting therapy without delay when the serum potassium value is above 6.5 even if the electrocardiographic findings are normal; we would suggest also considering the possibility of pseudohyperkalemia before undertaking therapy in these circumstances.

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Another Cause of Diarrhea in AIDS

TO THE EDITOR: Although patients with acquired immunodeficiency syndrome (AIDS) commonly have diarrhea, the incidence of *Mycobacterium avium-intracellulare* as a probable etiologic agent was first described only in 1983.[1] We now present yet another case of diarrhea secondary to this organism in a patient with AIDS.

Report of a Case

A 40-year-old bisexual man, an intravenous drug abuser, presented with a nine-month history of severe watery diarrhea five to ten times per day. He had a history of HbsAg-negative chronic active hepatitis, intermittent oral candidiasis and herpes, as well as shigella, amoeba, rectal gonorrhea, syphilis, rectal fissures and hemorrhoids. His outpatient work-up was negative for gonorrhea, chlamydia, syphilis, bacteria and ova and parasites, including cryptosporidium. Findings on flexible sigmoidoscopy were grossly normal.

On admission, the patient was cachectic, had splenomegaly and a leukocyte count of 2,300 per μl. A bone marrow biopsy specimen showed prominent collections of epithelioid histiocytes forming noncaseating granulomata. With special stains, multiple collections of acid-fast bacilli were seen. A sigmoid colon biopsy specimen showed a large number of foamy macrophages filling the lamina propria of the mucosa between the glands without distinct granulomata. However, acid-fast and periodic acid-Schiff stains showed many acid-fast organisms packing the cytoplasm of the foamy cells. Both tissues later grew *Mycobacterium avium-intracellulare.* The patient was initially treated with isoniazid and rifampin, but therapy later was changed to a regimen of chlorfazamine and ansomycin. Despite therapy, however, he expired.

Mycobacterium avium-intracellulare should be added to the host of other causes of diarrhea in a patient with AIDS.

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Emergency Room Physicians

TO THE EDITOR: I feel compelled to comment on the article by Sanders and Kobernick concerning the education of internists in emergency medicine.[1] No specialty wants to be any more restricted in its scope of practice than necessary. However, as a pediatrician, I find that internists make some of the worst emergency room physicians because they neither know pediatrics nor recognize their ignorance in that field. The curriculum proposed by Sanders and Kobernick gives only superficial coverage of pediatric emergencies. No mention is made of attempts to teach these physicians to diagnose and treat the more mundane but nonetheless important pediatric problems seen in emergency rooms. To expect a resident whose interest lies with adult medicine to absorb sufficient pediatrics in one to three months of training is unreasonable.

Likewise, I suspect that pediatricians would not be able to learn adult medicine under these circumstances. Training of internists for adult medical emergencies (and pediatricians for pediatric emergencies, and the like) is commendable. To believe that such training would allow internists, pediatricians or general surgeons to function well in a general emergency room is not only a fantasy but a dangerous one.

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Topics in Primary Care Medicine

Diabetic Foot Infections—Prevention and Treatment

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"Topics in Primary Care Medicine" presents articles on common diagnostic or therapeutic problems encountered in primary care practice. Physicians interested in contributing to the series are encouraged to contact the series' editors.

BERNARD LO, MD
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Infections of the feet are the most common reason that diabetic patients require admission to hospital. These infections cause an inordinate amount of morbidity and, on occasion, are responsible for the death of a patient. It is not generally appreciated that about 50% of all nontraumatic amputations of the legs in the United States occur in patients who have diabetes mellitus, attesting to the seriousness and frequency of these infections.

Predisposing Factors

A number of factors act in concert to predispose a person with diabetes to foot infections. These include peripheral neuropathies, occlusive vascular disease, microangiopathy, trauma, foot deformities—hammertoes, bunions, calluses—and impaired bacterial defense mechanisms. Functional abnormalities of neutrophils that have been identified in hyperglycemic patients with diabetes include impaired adhesiveness to blood vessels, abnormal chemotaxis and altered phagocytic, both ingestive and bactericidal, activity.

Classification

No standard classification exists for infections that involve the feet of diabetic persons. Traditionally, these infections have been characterized according to the primary tissue involved—skin and subcutaneous, fascia, muscle, bone—and whether they are associated with gangrene, gas or both. In another system, these infections are delineated according to the degree that surgical measures, in conjunction with antibiotics, are required to control them. There are infections of the feet that necessitate superficial debridement (ulcerations associated with cellulitis or purulent drainage), extensive surgical incision and drainage (necrotizing fasciitis, deep soft tissue abscesses, osteomyelitis) or radical excision (nonclostridial gas gangrene, synergistic necrotizing cellulitis).

Superficial Ulcers

A superficial foot ulcer that is unaccompanied by erythema, warmth or discharge is considered "noninfected." These lesions are painless and invariably contaminated by both aerobes and anaerobes. The identification of bacteria from the surface of the ulcer does not mean that the ulcer is infected and antibiotic therapy is indicated. In fact, no evidence exists that these noninfected superficial ulcerations are benefited by administering systemic antibiotics. The mainstays of therapy for these acute lesions consist of local debridement, correcting contributing external mechanical factors, mild elevation and applying a protective dressing. Local application of moist saline, povidone-iodine or zinc preparations, although frequently prescribed, has not been shown to expedite the rate of healing. When local swelling has subsided, the ulcer is classified as a chronic one and then may be treated in a plaster cast, permitting the patient to walk.

In conjunction with debridement, antibiotics constitute decisive treatment for a diabetic person with a foot ulcer complicated by cellulitis. Recent investigations indicate that these infections in diabetic persons are caused by a complex aerobic-anaerobic microflora.

Appropriate outpatient management includes chair and bed rest to elevate the foot and antibiotics given orally, such as clindamycin, 300 mg every six hours. If significant improvement does not occur in 48 to 72 hours, the patient should be admitted to hospital. Insignificant-appearing staphylococcal infections of the feet can result in bacteremia and infective endocarditis in diabetic patients.

Admission to hospital is indicated when toxicity or fever exists, when the infection is accompanied by significant soft tissue swelling or gangrene or when a patient cannot comply with home care. Needle aspiration of the discharge, accompa-

(Gleckman RA, Roth RM: Diabetic foot infections—Prevention and treatment [Topics in Primary Care Medicine]. West J Med 1985 Feb;142:263-265)

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nied by prompt Gram's staining and culture, facilitates determining the cause and guides initial antimicrobial therapy. When no exudate is present, the physician should inject a few milliliters of nonbacteriostatic saline into the inflamed skin and then promptly aspirate the fluid. The small amount of fluid retrieved should be inoculated onto culture media at the bedside.

Single-agent therapy, consisting of a 10- to 14-day course of intravenous administration of 2 grams of cefoxitin sodium every four hours, has been successful in treating these infections. For those patients who have had an immediate or accelerated hypersensitivity to a member of the penicillin family of drugs, an alternative treatment is indicated. This could consist of combining clindamycin—infused as 600 mg every six hours—and gentamicin—prescribed as 1.5 mg per kg of body weight given intravenously every eight hours after an initial dose of 1.75 mg per kg. The dose and interval for administering this aminoglycoside depend on a patient's renal function. Serum specimens should be assayed to assure achieving therapeutic concentrations of the gentamicin.

Foot ulcers complicated by cellulitis or sinuses should be assessed by x-ray film to detect concomitant deep tissue infections and osteomyelitis. Radionuclide imaging detects osteomyelitis earlier than conventional x-ray studies. The presence of concomitant cellulitis, however, will hinder interpretation of gallium scans. This problem can be somewhat remedied by analyzing early ("blood pool") and late ("uptake") imaging phases of the bone scan because osteomyelitis, unlike cellulitis, is associated with increasing radioactive uptake with time.

A team approach is often required to provide optimal care of a diabetic patient with a complicated lower extremity infection. Orthopedic or podiatric consultation, or both, is invaluable in formulating a diagnostic and therapeutic program.

In addition to antibiotic therapy and surgical procedures, treatment of infected feet in a person with diabetes is enhanced by achieving metabolic control. Insulin appears to correct some of the functional defects that occur in the leukocytes of a diabetic person and, presumably, it also promotes wound healing.

Chronic Osteomyelitis

In a diabetic person, chronic osteomyelitis involves predominantly the toes and small bones of the feet. The clinical presentation consists of pain, swelling and erythema or indolent ulcers, or a combination of these findings. The most common x-ray film evidence of chronic osteomyelitis in these patients is mottled lytic lesions. Initially, conservative therapy, consisting of the removal of all sequestra, devitalized tissue and sinus tracts, is attempted. Antibiotics should be infused for about six weeks, based on "valid" cultures obtained from a bone biopsy specimen. Culture of a sinus tract provides inaccurate identification of the bacterial cause of chronic osteomyelitis unless *Staphylococcus aureus* is found. Unfortunately, however, these infections are often recalcitrant to conservative treatment, and they continue to worsen. If an intensive course of parenteral antibiotics and conservative surgical therapy fail to eradicate the infection, a more radical surgical procedure is indicated to arrest the process and achieve a cure. The conventional approach has been a transmetatarsal, Syme's or a below-the-knee amputation. More recently efforts have been made to preserve a foot by combining antibiotic therapy with surgical removal of necrotic tissue and coverage by transferring vascularized tissue. Physicians should seek consultation from an orthopedic surgeon for guidance in the treatment plan. Consultation should be obtained early in the hospital course, as undue delay can result in extension of the infection, excessive hospital costs, inappropriate patient expectations and the need for a more extensive amputation.

Necrotizing Fasciitis

Diabetic persons with peripheral vascular disease are predisposed to have life-threatening soft tissue infections develop following trauma to the feet. These infections are listed in Table 1.

Necrotizing fasciitis is a rapidly worsening infection of subcutaneous tissue and fascia. A hot, tender, painful, swollen cellulitis progresses to crepitus, cyanosis, vesicle formation and gangrene. A systemic toxic condition and bacteremia usually occur. The diagnosis is established by the appearance of the necrotic fascia and undermined superficial fascia at the time of the surgical excision. A wide diversity of bacteria, including anaerobes, *S aureus*, aerobic hemolytic streptococci and Gram-negative aerobic bacilli, can be found. Therapy requires intravenous administration of antibiotics, extensive surgical excision, debridement and drainage and hemodynamic support. In most patients a repeat operation should be done within 24 hours of the initial debridement to identify and remove all the infected tissue. A combination of gentamicin and clindamycin is appropriate initial antibiotic treatment, to be modified according to the results of intraoperative cultures.

Nonclostridial Gangrene

In diabetic patients, gangrenous infected lesions of the feet accompanied by subcutaneous gas are usually nonclostridial. Compared with clostridial myonecrosis, there is less pain and toxicity and slower spread of gangrene. The microbiologic complex of nonclostridial gas gangrene consists of anaerobes, enterococci and Gram-negative aerobic bacilli. Antibiotic treatment consists of a combination of metronidazole or clindamycin, ampicillin and an aminoglycoside. Surgical excision, usually amputation, is required.

TABLE 1.—*Unusual Life-Threatening Soft Tissue Foot Infections in Cases of Diabetes Mellitus*

Infection	*Tissue*	*Clinical Manifestations*
Necrotizing fasciitis	Fascia, subcutaneous tissue	Rapidly spreading, painful cellulitis and dermal gangrene; systemic toxicity; occasional crepitus, and local anesthesia
Synergistic necrotizing cellulitis	Primarily fascia and muscle	Rapidly spreading, painful dermal gangrene and ulcers draining "dishwater pus"; occasional crepitus; no local anesthesia; systemic toxicity
Nonclostridial gangrene	Skin, subcutaneous tissue and muscle	Moderately progressive; modest toxicity; mild tenderness; minimal skin discoloration; significant crepitus

Synergistic Necrotizing Cellulitis

Synergistic necrotizing cellulitis is a life-threatening soft tissue infection that primarily involves fascia *and* muscle and secondarily affects subcutaneous tissue and skin. Exquisitely tender, necrotic skin lesions develop that exude a foul-smelling, reddish brown fluid, referred to as "dishwater pus." A systemic toxic reaction invariably occurs, and some patients have tissue gas and bacteremia. Gram-negative aerobic bacilli and anaerobes are consistently recovered from these infections. In terms of the clinical manifestations, rapid spread of the infection, microbiology and treatment, this infection often resembles necrotizing fasciitis. Therapy consists of fluids given intravenously, antibiotics and excision of all infected tissue. An appropriate antibiotic combination is an aminoglycoside and either metronidazole or clindamycin.

Prevention

Patient education is the cornerstone for preventing foot infections. Physicians should instruct their patients to inspect their feet on a daily basis; a mirror can help in detecting abnormalities of the plantar surface. The detection of any abnormality, including minor foot irritations, erythema, edema or calluses, necessitates prompt evaluation by a physician or podiatrist. For a visually impaired person with diabetes, a member of the patient's family can inspect the feet. The feet should be soaked in warm, never hot, water for 15 to 20 minutes a day and then dried thoroughly. Petroleum jelly is rubbed over the skin to prevent evaporation of the absorbed moisture. Excessive heat, chemical irritants and walking barefoot are to be strictly avoided. Proper trimming of the toenails is important in preventing local infections, and this activity can be done by a trained professional if the patient or family member is unable to do the task satisfactorily. New shoes can be a particular problem for a diabetic patient with peripheral neuropathy, and the hazards of improperly fitted shoes need to be carefully explained to patients. A new shoe should be worn for only two or three hours on the first day and the feet subsequently inspected for evidence of erythema or heat. Diabetic persons should be advised to wear only leather shoes because vinyl and other plastic materials do not readily adapt to relieve local pressure. On occasion, specially designed and constructed shoes may be indicated.

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Commentary

On the Superiority of Women

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Consider for a moment the *Labroides dimidiatus*, found swimming in the blue waters off Australia's Great Barrier Reef. We would surmise that for the male *Labroides*, surrounded by a harem of eight or nine females, life in these tropical waters would be a piscatorial paradise.

But through a biological quirk this fellow is doomed to a short and unhappy life. The dominant female in his harem sets out to make his life totally miserable, filling his days with stress and harassment, until the poor male simply gives up and dies. Then, through a bit of hermaphroditic magic, the female takes over the male role, ruling over the harem and eventually becoming a functional male.

This story, innocently interjected into the conversation in the doctors' lounge, brought a chauvinistic response: "Now, that's just what the female libbers are trying to do!"

To that I cannot agree. But I do pause to wonder why any female member of the human species would want to emulate the male when there is such an abundance of evidence indicating that she is so far superior to her male counterpart. She outdistances him, outperforms him throughout life, surpassing him from the moment of conception to the hour of death.

Even before life begins, there is female superiority. The Y-type male sperm may swim a bit faster, may be a little more aggressive, but in the long run the X-type female sperm outlasts the male, being more durable, more patient in achieving its designated task.

It is true that the eager, fast-moving male sperm does manage to impregnate a higher percentage of ova, with the result that there are between 120 and 140 male conceptions for every 100 females. But that proves to be an empty victory. More males are spontaneously aborted during pregnancy, and more males are stillborn. Estelle Ramey, professor of physiology and biophysics at Georgetown University School of Medicine, attributes this to the female's inherent sex-linked resistance to life-threatening disease.

Embryologists have informed us that the basic plan of the mammalian organism is female, and elaborate intrauterine transformation must take place to produce a male fetus. It is notable that 33% more male fetuses are born with congenital defects, very likely because something went wrong during the embryo's complicated transformation from femaleness to maleness.

Once out of the uterus, the female superiority continues. Boy babies have a higher incidence of hyaline membrane disease. The lungs of the female fetus mature two weeks earlier than those of the male, probably benefited by a higher level of female hormone.

The female fetus seems more able to withstand the rigors of the passage through the birth canal. Brain damage secondary to birth trauma has a more debilitating effect on boys.

All these biological facts cast a long shadow over the life span of the female as she grows to maturity.

The female child matures physiologically, emotionally and socially at a much earlier age. Girls go through the socialization process much earlier and are "social beings" throughout their lifetime. Women experience a gradual rise in what psychologists term "sexual arousability," peaking around the age of 30 and remaining at a fairly constant level thereafter.[1(p576)]

When the headlines shout that "Heart Disease Is Mankind's Public Enemy No. 1," they are, in fact, referring to men. Women's hearts are healthier. Rarely do we hear of premenopausal women suffering heart attacks. There is now evidence suggesting that the female hormone, estrogen, protects women against coronary disease[2]; it is hypothesized that high estrogen levels increase the circulating high-density lipids (HDL) and thereby help prevent atherosclerosis.[3]

All this, in part, accounts for the increased life expectancy of women. A baby boy born today can look forward to 70.7 years of life on this planet; a baby girl has a life expectancy of 78.2 years.

There now seems to be mounting evidence that the female brain is anatomically different and in some ways physiologically superior to that of the male. Verbal skills are thought to be governed primarily by the brain's left hemisphere.[4] Because the female appears to make better use of that half of her brain, she is more communicative, more sensitive to context, more interested in people—again, a more social being.

The gender differences go even further. Specifically, in a woman's brain there is better communication, better crossover between the two hemispheres; therefore, damage to one hemisphere, should it occur, is less devastating than it is for a man. This may be why dyslexia and learning disabilities occur more often in the male.

There are extenuating factors, of course. The special attri-

(Fox ERW: On the superiority of women [Commentary]. West J Med 1985 Feb; 142:266-267)

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butes of the right hemisphere of a male brain make men more adept at visual-spatial tasks, excelling at manipulating *things*, at jobs that require manual dexterity. Men are the aggressive hunters, the bruising football players. The male brain seems to handle analytical and mathematical problems more easily.

Yet, as the 20th century nears its close, the gender gap begins to narrow. More women are seen in the ranks of architects and engineers. Girls are insisting on places on football teams. Women are flexing their political muscles: Connecticut elected a woman governor in 1974 (the first elected on her own record—that is, not replacing a deceased husband) and Washington state did in 1976. Kentucky now has a woman governor, and a half dozen major cities have women mayors. Now there are only "eight old men" on the Supreme Court, with one smart and handsome young woman serving as an associate justice. And in 1984 a women for the first time was nominated for Vice President on a major political ticket.

The US Census Bureau reports that not only does our nation's population grow older, it grows more female. Are we, in the next century, to see an evolutionary shift to female predominance? Generations down the road of life are we to see proof of the theory that ontogeny recapitulates phylogeny—to go the way of the male *Labroides dimidiatus?*

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They All Laughed When I Spoke of Greedy Doctors

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At the 110th Annual Meeting of the Oregon Medical Association, a respected colleague, Dr Leigh C. Dolin of Astoria, proposed that the state medical association join him in deploring the unreasonably high fees of some physicians. It seemed like an appropriate idea to me and I made a point to be present at the reference committee meeting to take part in the general testimony.

Consideration of the resolution followed a heated debate on cognitive versus procedural reimbursement. This involuntarily gave a slant to the discussion concerning reasonable fees, for when introducing his resolution Dr Dolin contrasted the reimbursement of a pediatrician working up a child for an appendectomy with that of the surgeon who removed the offending organ. Any merit I had given his resolution began evaporating as the debate focused on who was to get the most, the pediatrician or the surgeon. What had brought me to the hearing was the problem of greed within the profession, independent of specialty, in which a small proportion of the practitioners lack moral compunction about charging all that the traffic can bear. As one physician put it, perhaps as a slip of the tongue, "They practice money and make medicine."

The words about relative reimbursement began to sound like the growling of dogs over a bone, lacking concern for the carcass the bone came from. Hoping to focus the problem on causes deeper than relative reimbursement, I took my place in the line behind the microphone and when my turn came declared, "I speak in favor of the resolution since it addresses one of the critical problems of the medical profession, physician greed. I suggest the reference committee refer this problem to the Impaired Physicians Committee for study and action."

The room broke into laughter and when the hooting and hollering subsided I went on, "Look, today the central clinical problem we physicians face in practice is appetite control. Patients seem insatiably hungry for cigarettes, food, sex, money, work, love and pills. Are we so different from our patients? Consider what we have been able to do through the Impaired Physicians Committee for these doctors with a malignant appetite for alcohol and other mind-altering drugs. We have an incidence of drug addiction which runs 100 times higher than that for a comparable lay population. This is because we work hard and have practically unlimited access to mind-altering drugs. Does the same not apply to money? With hard work and inflation we are exposed to the danger of greed as never before. I think the Impaired Physicians Committee should take a look at what is going on with these sky-high-fee practitioners."

Well, the chuckles continued as I sat down and I well know what it is to be "the laughingstock of your peers," but if anyone took a close look at a money-impaired physician, I doubt that the smiles would last. There he is, never seeing patients, only customers. No free care given by him. The poor get a no-nonsense command to go elsewhere. With his lust for a buck, the money-impaired doctor is a menace to the profession.

However, the subject proved moot and unactionable since the Association's attorney took the floor as a point of order and informed us we were acting illegally according to Federal Trade Commission regulations in raising the subject of particular fees in an organized professional meeting. The subject was immediately dropped but left me thinking that someplace in Washington, DC, there must be a mighty powerful rich man's lobby at work since now it is against the law to talk about pirates.

(Crawshaw R: They all laughed when I spoke of greedy doctors [Commentary]. West J Med 1985 Feb; 142:267)

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Information

Health Screening of Physicians
A Role for Local Medical Societies

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A SUBSTANTIAL LITERATURE describes the unique problems that occur when physicians become patients. Courtesy treatment may make physicians reluctant to impose on their colleagues.[1-3] Doctors are thought to be difficult patients and may receive less than optimal care.[1,4,7] Many doctors treat themselves.[8] Although physicians have a lower mortality rate than the general population, they have an increased prevalence of coronary artery and cerebrovascular disease,[9] and thus may be especially in need of preventive health services. Yet relatively few doctors have a regular physician who could provide these services.[5]

Professional organizations, such as county medical societies, have developed programs for impaired physicians—that is, those whose medical practice is affected by drug or alcohol abuse.[10-12] In part, these programs exist because of the recognition that such health problems affect not only the impaired physicians but also the patients they care for. By contrast, little information exists concerning organized programs that address more comprehensive health care needs of physicians. Yet evidence is accumulating to suggest that physicians' personal health care practices also affect their practice of medicine.[13]

In this paper, we describe the programs developed by county medical societies to provide comprehensive health screening for their members. For one of these programs we determine the prevalence of program use, the yield of positive physical findings and the follow-up behavior of physicians with positive findings. To do this, we use three data sources: a survey of a random selection of US county medical societies, the examination data from the health screening program of one medical society and a follow-up survey of members of that medical society.

(Wells KB, Lewis CE, Potter RW: Health screening of physicians—A role for local medical societies [Information]. West J Med 1985 Feb; 142:268-270)

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This study was supported in part by a grant from the Robert Wood Johnson Foundation. The opinions, conclusions and proposals in the article are those of the authors and do not necessarily represent the views of the Robert Wood Johnson Foundation.

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Survey of County Medical Societies

Our sample of medical societies included state societies of the nine states with no county medical societies, 100% of county medical societies with membership of 1,000 or more, a 20% random sample of societies with membership of 100 to 999 and a 30% random sample of societies with membership less than 100. The 149 selected societies were sent a cover letter that included a description of a comprehensive health screening program for physicians sponsored by the Fresno-Madera County Medical Society of California[14] with whom the authors were consulting. A questionnaire asked, (1) Do you know of current or past programs designed to meet comprehensive health needs (similar to the described program)? and (2) Do you know of attempts to develop such programs which aborted or were unsuccessful? Societies answering yes to either question were asked to give detailed information. This information was verified by contacting the director for each identified program.

Eighty-six societies returned questionnaires for a response rate of 58%. Thirteen societies knew of a current or past program that concerned the health needs of physicians. Eight separate programs were identified. Six of these programs included physical examinations or laboratory studies, or both. Only three of these were still operating in 1978. Thus, such organized health screening programs are of very low prevalence.

These three programs had several common characteristics. All were in societies of 750 members of more. The programs were held every year or two, over a 2-day to 12-day period. Appointments for examinations were made individually. Records were kept confidential and were mailed back to physician participants. Local hospitals and technicians donated their services or were partially reimbursed by physician payments or local drug companies. One highly motivated member or society president started and supported each program. Support of the program by physicians' spouses was seen as key to program success.

Programs that had been terminated indicated that general lack of membership support (three societies) or lack of belief in the value of "routine screening" (one society) or lack of a program administrator (one program) were key reasons for failure.

Health Results

We reviewed the records of the comprehensive health screening examination of the Fresno-Madera County Medical Society for the year 1978. Data sources included a self-report checklist of past and current health problems, findings from 19 physical examination stations, including sigmoidoscopy, otology and ophthalmology, and the results of complete blood counts, a blood chemistry panel, urinalysis, electrocardiogram, chest x-ray and pulmonary function tests. Psychiatric assessments were provided but not recorded. Master problem lists of current (nonredun-

dant) health problems for each participant were derived from the complete record by a committee of physicians from the society. Additional demographic information on all society members was available from the society directory.

A total of 153 members (25% of the society) participated in the program in 1978. The distribution of age and specialty of participants was not significantly different from that of all members of the society at the .05 level (χ^2 test). Of participants, 93% had physical examinations. Only 7% of participants had no current health problems recorded on the master problem list. Table 1 gives the percent of physicians with selected most prevalent health problems. Roughly 25% of physicians were grossly overweight on examination, had high diastolic blood pressure or abnormal serum lipid values. Nearly a third had subnormal hearing.

There were several potentially serious but uncommon problems detected during the examination, including 13 suspicious skin lesions, six rectal polyps, seven prostate nodules, three suspicious breast masses, one ovarian mass and one case of sarcoidosis.

Follow-up Survey

In 1979 we delivered a self-report questionnaire to the offices of a random sample (N = 201) of the members of the Fresno-Madera County Medical Society, who practiced in the following specialties: family practice, internal medicine (and related subspecialties) and surgery (and related subspecialties). The questionnaire elicited information on specialty, board certification, years of program participation (1974, 1976, 1978), reasons for use or nonuse of the program, whether new health information was obtained from the program and the nature of any follow-up taken.

In all, 151 questionnaires were returned, for a response rate of 75%. Respondents did not differ significantly at the .05 level from nonrespondents in specialty or age distribution. Of the respondents, 50% had been examined at least once in the program.

Those who *never* participated in the program indicated three reasons for nonparticipation: having a regular physician (47%), feeling well (24%) and unfamiliarity with the program (16%).

Of the 74 respondents who *ever* participated, 95% indicated that they felt well but wanted a complete physical. Only eight physicians reported feeling ill as a reason for participation. There were 51% of the participants who learned new information about their health as a result. Of those who learned new information, 89% made some follow-up. Of these, 35% treated themselves, 30% contacted their regular physicians and 35% made a new contact with a colleague for evaluation.

TABLE 1.—*Percent of Participants With Selected Health Problems*

Health Problem	*Percent of Participants*
Any problem	93
Significant obesity*	25
Diastolic blood pressure more than 90 mm of mercury	21
Abnormal pulmonary function tests†	46
High blood cholesterol†	22
Low HDL cholesterol†	15
High serum triglycerides†	20
Abnormal audiometry†	32

Total participants = 158

*As perceived by the examiner.
†Out of the range of normal for the reporting laboratory.

Discussion

Our first objective was to determine the extent to which organized medical societies have attempted to provide health screening for their physician members. From a survey of a random sample of county and state medical societies, we found that only a handful of such programs have existed in the last decade, and most had been discontinued before 1978. Our description of these programs may provide guidelines for those societies interested in developing such programs in the future. In particular, treating each physician as an individual (appointments, privacy during examinations) and maintaining confidentiality of results appear to be essential to program success. Exchange of examination teams among societies and election of examiners are but two strategies that might increase the doctor/patient's sense of privacy.

Our second objective was to determine if such programs are effective in identifying new health information for physicians, and if follow-up is made. Our study of one society program indicates that half of those who participated learned new health information and that most of these made some follow-up. Consistent with findings of other studies,[8] a substantial proportion chose to treat themselves.

The yield of positive findings in the Fresno program is much higher than that reported for comprehensive screening in a general population.[15,16] For example, Olsen, Kane and Proctor[15] reported a positive yield of 8% for audiometry, 5% for high blood pressure and 4% for abnormal serum triglycerides or cholesterol in their evaluation of a general low-income and middle-income population. Our results are more similar to those reported for populations referred by their physicians either for general health screening or for workup of specific health problems.[17,18] The high positive yield in our study may be partly due to the ability of physicians to appropriately select themselves for a health screening program. Alternatively, the high yield may reflect a high prevalence in the physician population of cardiovascular disease and risk factors. This interpretation is consistent with studies that report increased cardiovascular risk in physicians.[9]

As much as physicians have been admonished to "heal thyself," the realities of practice, personalities of physicians or other factors may preclude adequate health care for physicians. Our results suggest that medical societies rarely facilitate the difficult role shift from physician to patient, in part because of doubts about the value of routine screening. Recent policy statements by several groups of physicians recommend reserving the use of screening for particular clinical indications (for example, patient age or risk factors).

Screening programs in medical societies may be more readily accepted by their members if such specific recommendations are followed. Our case study of one program

suggests that when used, such programs may have a meaningful impact on physicians' knowledge of their health problems and on the medical care they seek for these problems. It may behoove administrators of medical societies and organizers of continuing education conferences to reexamine their potential contributions in meeting such personal needs, in addition to the professional services they provide.

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Care of Uncircumcised Children

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THE AMERICAN ACADEMY OF PEDIATRICS' TASK FORCE on Circumcision issued position papers in 1971 and 1975 stating "that there are no valid medical indications for circumcision in the neonatal period."[1] The position paper stated that it is the responsibility of physicians to provide parents with information on which to base an informed consent. They recognized that "if circumcision is not elected, the necessity for life-long penile hygiene should be discussed with the parents, preferably before the birth of the infant." They went on to conclude that a "program of education leading to continuing good personal hygiene would offer all the advantages of routine circumcision without the attendant surgical risk." However, the program of education alluded to has never been outlined and standards of care for the uncircumcised child have never been published.

The intent of this paper is to review literature that will help physicians assist their patients in making fully informed decisions and provide the basis for sound hygienic counseling.

Current Status

The lack of information in the literature on care of uncircumcised infants translates into a lack of knowledge on the part of those physicians caring for these infants. One study involving 90 pediatricians showed that 47% felt the foreskin should retract easily at 6 months of age.[2] In the same study, mothers of infants were contacted after hospital discharge. For circumcised infants, 85% of mothers stated they had been given instructions for hygienic care. Of the mothers of uncircumcised infants, half were given no advice concerning hygienic care of the penis. The remaining half were told to retract the foreskin during the daily bath, but none were told when the foreskin should be fully retractable. Seven infants had manipulation of preputial adhesions during the first six months of life, and three of these mothers were dissatisfied with their decision not to circumcise. These mothers felt uncomfortable with the required hygienic care, and stated that they would choose to have circumcision on subsequent male infants. Another study identified three families in which a male child had not been circumcised, with subsequent delivery of another male infant. The parents elected to have the second male circumcised in two of these three instances.[3]

Several factors may be contributing to the continuing high rate of neonatal circumcision. Physician resistance is evident from the debate in the literature regarding the merits of neonatal circumcision. There are arguments that optimal hygiene may be more of an ideal than a reality. It has been postulated that the risk estimates for cancer of the penis, which occurs almost exclusively in uncircumcised men, have been significantly underestimated in population-based studies of predominantly circumcised men.[4] It is possible that urinary tract infections during infancy are more frequent in uncircumcised male children than in the circumcised ones.[5] Some argue that the frequency of circumcision later in life justifies neonatal circumcision.[6] Physicians convinced that neonatal circumcision is unwarranted face the problem of parental request for the procedure. Two studies have shown that educational intervention with parents has been relatively ineffective in altering the high rate of neonatal circumcision.[7,8]

Physicians may be encountering a higher percentage of uncircumcised male children. Economic and social influences which may decrease the incidence of neonatal circumcision include early hospital discharge, withdrawal of third-party payer reimbursement and increased parent awareness about current recommendations from media sources, childbirth education classes and physician counseling. Therefore, physicians caring for infants should be familiar with the prepuce in its natural state. Some background information about circumcision and preputial development provides a context for caring for these patients and counseling their parents.

(Fox GN: Care of uncircumcised children [Information]. West J Med 1985 Feb; 142:270-272)

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History

The origins of circumcision are unknown and its practice differed in the diverse cultures in which it arose. It has been postulated that circumcision may have originated with a heliolithic culture which, some 15,000 years ago, spread out over much of the world. Circumcision has been practiced by Jews, Moslems and selected tribes in Australia, Africa and the Americas. Circumcision was not uniformly performed neonatally; it was a rite of puberty in some cultures. Females were also circumcised in some societies.

Hygiene did not appear to be a prominent theme in the known evolution of circumcision. In ancient Egypt captured warriors were often mutilated to mark them as slaves; circumcision was one of the procedures used for this purpose. The ritualistic circumcision adopted as a Judaic custom thus may have arisen while the Jews were enslaved in Egypt. The ritual became incorporated into the Old Testament as a covenant between God and man.[6]

Circumcision was introduced into Europe with the spread of the Roman Empire and Christianity. Little is known about the extent of the practice in Europe during that era or during the Middle Ages except that circumcision was maintained as a Judaic religious rite. With the advent of modern surgery, the status of neonatal circumcision in the United States changed from that of a religious rite to that of a common surgical procedure with several current series reflecting a rate in excess of 90%.[2,7,8]

Anatomy

Figures 1 and 2 illustrate the important anatomical landmarks.

Embryology

Near the end of the first trimester, the genital swellings are differentiating into recognizable male external genitalia.[9] The genital tubercle elongates into a structure called the phallus. By the end of the first trimester, a groove has formed on the distal phallus at the level of the coronal sulcus. A roll of epithelium, incomplete ventrally, forms at this area, and advances forward over the glans to form the foreskin. Fusion of this tissue takes place ventrally in the midline. At birth the frenulum and ventral line of fusion are recognizable remnants of the embryologic past. Although prepuce and glans have separate epithelial surfaces, these two epithelia fuse. Later separation of these occurs as the cells in the fused layers mature and desquamate. This process results in retractability of the foreskin. This preputial separation occurs along an age-related continuum, with approximately 4% of males having retractable foreskins at birth and only 3% retaining adhesions by 16 or 17 years of age. (The term "adhesion" usually denotes a pathologic process. Some authors object to its use in reference to preputial nonseparation since this process reflects normal development.)

Natural History

Two studies have been published regarding the natural history of postnatal preputial adhesions. Gairdner's data were obtained on British children.[10] His data are uncorrected for circumcision (about 10%) and for medical manipulation of the adherent prepuce (unknown percentage). His uncorrected data reflect age-specific incidences of fully retractable foreskins of 20% at 6 months, 50% at 2 years and about 90% at 4 to 5 years of age. A group of uncircumcised boys aged 5 to 13 years was studied separately, and 6% had a nonretractable prepuce, while 14% had partially retractable foreskins with persistence of adhesions. Breakdown of data by age was not presented for this group. It was noted that inspissated smegma seemed more frequent in this group than in the younger children.

Oster studied Danish school children.[11] He states that circumcision and prior manipulation of the prepuce were minor

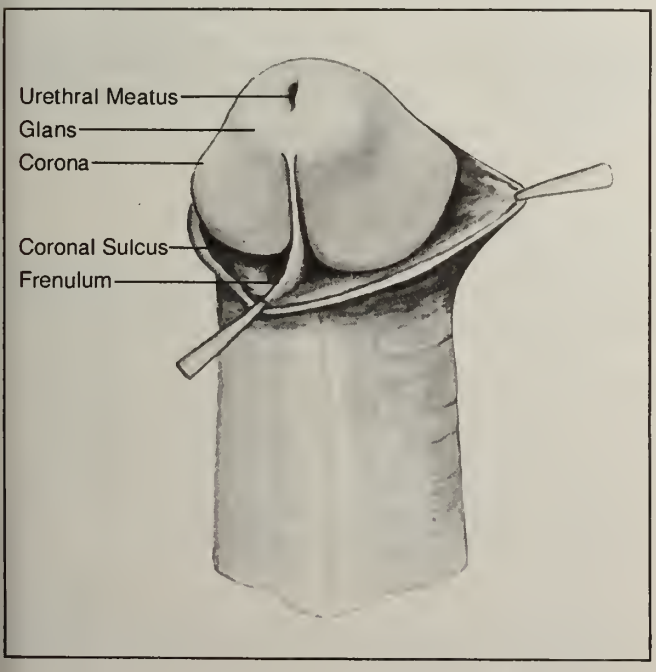

Figure 1.—Cut-away illustrating anatomic landmarks.

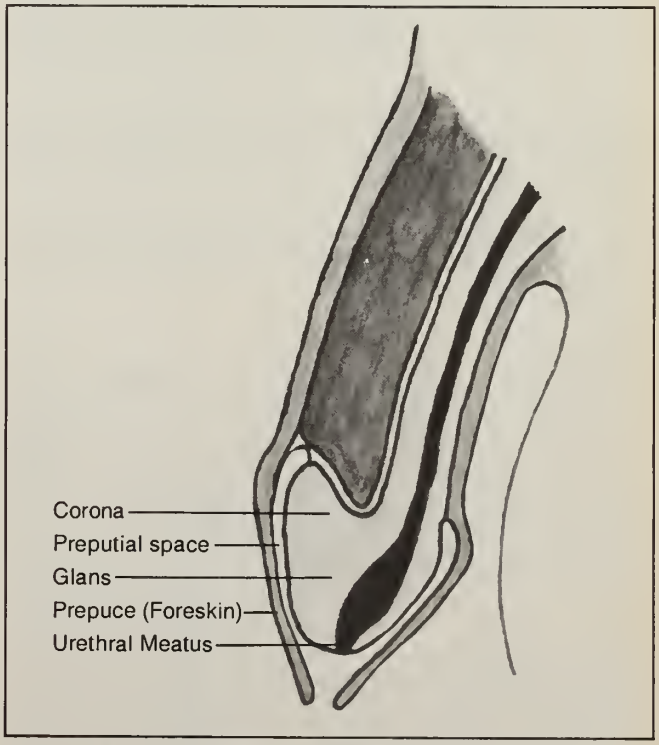

Figure 2.—Median section illustrating anatomic landmarks.

problems in his study because Danish tradition mandated no interference in this regard. Oster's data, summarized in Table 1, illustrate the striking continuation of natural preputial separation late into the teenage years. The term "phimosis" implied that the prepuce could not be retracted by gentle manipulation. "Tight prepuce" indicated that there was slight difficulty with retraction. Preputial adhesions were assessed in those cases in which no phimosis was present. Incomplete retraction was observed in approximately 65% of 6 to 7 year olds, 50% of 10 to 11 year olds and 15% of 14 to 15 year olds. The rate of resolution of adhesions was still pronounced in the teen years, decreasing from 33% at ages 12 and 13 to 3% at 16 and 17. Smegma was also assessed in this study and rose from 1% of boys in the 6 through 9 age groups to 8% in the 14 through 17 age groups. In a subgroup of 173 boys examined annually for seven successive years, phimosis developed in three between the ages of 10 and 12 years. Surgical procedures were required in these instances. Four of the 173 boys had their prepuces manipulated by a physician, and in none of these children did problems develop.

TABLE 1.—*Age and Preputial Status*

Age Group (Years)	*No. of Observations*	*% With Phimosis*	*% With Tight Prepuce*	*% With Adhesions*	*% With Incomplete Retraction*
6-7	591	8	1	58	66
8-9	1,374	6	2	55	61
10-11 . . .	1,662	6	2	45	51
12-13 . . .	2,523	3	3	33	36
14-15 . . .	2,744	1	1	13	14
16-17 . . .	651	1	1	3	4
Total . .	9,545				

Unanswered Questions

Some questions have not been answered regarding care of uncircumcised children. There are no data to support physician intervention, such as lysis of adhesions or dilation of the preputial orifice. On the other hand, there are no data showing these procedures to be harmful or ineffective. Should these procedures be considered, there is no information regarding indications for performance, optimum timing or the need for repeat procedures or subsequent circumcision. There is uncertainty as to factors responsible for the development of unphysiologic secondary phimosis. Optimum timing for carrying out circumcision for continued phimosis or tight prepuce is also not clear. It has been recommended that preputial nonseparation persisting to school age is an indication for circumcision.[12] From the studies cited, at least 10% of boys would then require circumcision around 5 years of age. Nonintervention until age 15 to 17, however, would be expected to reduce the circumcision rate to 1% or 2% for this indication. The psychological impact of neonatal, preschool and late teenage circumcision is an important factor in this decision and remains to be elucidated. Explicit analysis of cost and risk of the procedure in newborn infants, preschool children and teenagers also remains to be done to complete the analysis of optimum timing.

Conclusions

In spite of these limitations, certain recommendations and instructions can be given to parents:

1. In an uncircumcised infant, there is no evidence that medical manipulation of the prepuce (such as lysis of adhesions or dilation of preputial orifice) is beneficial.

2. At school age, approximately 10% of boys will have nonretractable foreskins, and more than 50% may have some adhesions. By the late teenage years, these percentages decrease by about a factor of ten (about 1% and 5%, respectively). The parents need to be psychologically prepared for preputial nonseparation during infancy and, in some cases, into the teen years. Preconceived timetables for full retractability may need to be discussed.

3. Any myths regarding symptoms that historically have been blamed on the foreskin should be dispelled. There is no evidence for an increased frequency of enuresis, fondling of genitals or other problems secondary to presence of the foreskin.

4. The parents, when bathing the child, should gently retract the foreskin. No force need be (or should be) applied. When the child is old enough to participate in self-care, gentle retraction and washing should be taught. In order for adequate penile hygiene to be practiced in an uncircumcised child, the parents and the child must be comfortable with bathing and proper hygiene, including handling of the genitalia. Smegma is rare before the foreskin is fully retractable, so concern about this development is not warranted. (The threadlike whitish bands of adhesions should not be confused with smegma.)

5. In some males it later becomes necessary to perform a circumcision for a variety of reasons. It is impossible at birth to predict who will require this operation. While certain problems may develop that require circumcision at a particular time, it is currently unclear what the optimal age is for circumcision for preputial nonseparation.

6. Paraphimosis is best treated by prevention. When the foreskin is almost fully retractable, but tight, it should not be forced over the corona. When the foreskin is retractable, it should always be returned to its normal position.

7. In selected instances, such as where hygiene is suspected to be a significant problem, or where there is a very strong family history for diabetes mellitus, neonatal circumcision may be a consideration because of an increased risk for requiring the procedure later in life.

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Book Reviews

The Western Journal of Medicine *does not review all books sent by publishers, although information about new books received is printed elsewhere in the journal as space permits. Prices quoted are those given by the publishers.*

THE AMA AND U.S. HEALTH POLICY SINCE 1940—Frank D. Campion. Chicago Review Press, 820 North Franklin Street, Chicago, IL 60610, 1984. 538 pages, $25

I have just finished reading a recently published book entitled *The AMA and U.S. Health Policy* by Frank Campion. Campion was originally an editor for *Life* magazine and has been with the AMA staff since 1970. The book is primarily an account of happenings within the AMA since 1940, but it is far more than this. It is an excellent analysis of the forces that have conspired to create the present-day medical environment.

Campion begins with a description of the development, in the early 1900s, of our pluralistic health care delivery system founded on a laissez faire economy that created the most affluent middle class in history, along with a mistrust of government in general. Medical institutions were largely privately financed (only 20% had government funding) and as sociologist Oden Anderson points out, "The American hospitals were subsidized, without interest, or thought of repayment by the newly rich and not so rich."

This era ended with the Great Depression which virtually eliminated the affluent middle class and invited the early government intrusion into medical care. Also examined are the World War II and postwar eras of tremendous scientific advances, burgeoning specialization and seemingly inexhaustible government funding that irrevocably altered the course of medical care. Finally the present day socioeconomic scene of Medicare, Medicaid, FTC and PROs—which we all know too well—is scrutinized.

The book is alive with the people who have labored in the vineyards of organized medicine. Washington state's Bob Hunter reminisces, "Like my father, I have wanted above all to be a good physician. But I have also wanted to do some things on behalf of the profession and some things that I would consider to be on behalf of the people as a whole." One chapter is devoted entirely to Morris Fishbein, the gifted editor of *JAMA*, who was for several decades "Mr AMA." During much of that time the AMA was almost totally supported by income from *JAMA* and no dues were collected; consequently the editor had tremendous influence. Fishbein never held an elected office in the AMA but no one has been as powerful in the organization before or since.

There is one quotation that captures the essence of what membership in both the AMA and our state medical associations is all about. One longtime member says, "Joining the AMA is like joining a church. You don't do it because it pays or because you have to. You join it because you believe in it."

This is an excellent book because it outlines so clearly the medical heritage upon which we must build our future. I recommend it to all.

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HUMAN SEXUALITY AND ITS PROBLEMS—John Bancroft, MD, MRCP, FRCPsych, MRC Reproductive Biology Unit, Edinburgh; with the assistance of Philip Myerscough, FRCS(Ed), FRCOG, Royal Infirmary, Edinburgh. Churchill Livingstone, Inc., 1560 Broadway, New York, NY 10036, 1983. 448 pages, $24.95.

In writing *Human Sexuality and Its Problems,* Dr John Bancroft has undertaken a monumental task of systematically reviewing both empirical and clinical literature on human sexuality. His approach encompasses both factual knowledge, clinical interventions and clinical wisdom. The book is primarily intended for health professionals who have interest in working with sexual problems but is also designed to be sufficiently broad to serve as a comprehensive text for those being introduced to the field.

Knowledge of human sexuality has expanded exponentially over the three decades since the initial Kinsey studies. Contributions to this understanding have come from anthropology, biology, physiology, psychology, sociology, medicine and virtually every other scientific discipline. Hence, the task of reviewing this body of literature in any comprehensive way and integrating it into a systematic and understandable text is extremely difficult. Dr Bancroft has accomplished this task remarkably well. One will find, in this book, a surprising amount of depth. Concepts from man's evolutionary past, cultural heritage and genetic endowments are all well integrated with current behavioral and social systems theory. While this degree of comprehensiveness does not allow the indepth coverage of some topics that more specialized texts might provide, it is very difficult to fault the author for being inappropriately shortsighted in any topical area. He shows a wide range of familiarity with both specialized surgical procedures, psychological views of diagnosis and treatment, and social-biological views of the role of sexuality in the human experience.

The author has systematically excluded or minimized in this text psychoanalytic and certain other philosophical approaches to human sexuality. In doing so, however, it is clear that this does not represent an oversight but rather, is a systematic effort to approach the topic in the most scholarly fashion. Dr Bancroft is explicit about his desire to stay within the mainstream of conventional scientific scholarship. It is on this latter basis that he systematically excludes intensive assessment or integration of Freudian theory with the facts presented throughout the book. He maintains that psychoanalytic viewpoints have erected many barriers to scientific process and elects, therefore, to make his presentation primarily with literature based in the scientific method and the spirit of empirical rather than philosophical investigation. While one may disagree with this point of view, its adoption does lend a degree of consistency to the volume which would otherwise not be possible.

It is also remarkable, even in a field as highly colored by moralities as sexual functioning, to find an author who is as willing as Dr Bancroft to be direct about both his philosophical and moral positions. These positions are stated straightforwardly, at the outset, and serve as precursors to developing a line of reasoning that subsequently permeates the entire volume. The author is very explicit about his own morality relative to the use of sexuality for recreational purposes. His explicitness about his own viewpoint lends a certain degree of credibility to his presentation which one cannot help but find to be refreshing. Again, while one may disagree with the author's particular morality, being aware of it at the outset of the volume assists one in assessing the interpretations which are lent to the multitude of facts and empirical investigations reviewed. For example, with an understanding of the author's moral viewpoint, his great cautiousness in recommending surgical correction for erectile failure disorders and his contrasting liberality in the acceptance of sexual surrogates become more understandable. Surprisingly, there are few areas in which one can specifically point to the author's intrusion of his own belief systems into his representation of the facts and empirical data. This book presents an intriguingly balanced approach to the issue of human sexuality and its treatments.

If the volume is to be criticized, which it need not be, it can be done so on only two grounds. First, the proofreading of the volume is somewhat sloppy and often distracting. There are numerous typographical errors which are only compounded for American readers by the differences in spelling between the English and the American presentations. Second, the effort to

accomplish breadth sacrifices depth. For example, while his expressions of concern about the value of nocturnal penile tumescence as a diagnostic indicator in erectile failure disorders are interesting and provocative, they are not complete. There is considerably more literature in this area to validate the importance of this procedure than that to which the author has given attention. The same can be said for several other areas. On balance, however, the author has taken the better tactic in providing a comprehensive view of the field rather than an intensive view of any particular area. Moreover, his conclusions, even in those areas which are not comprehensively reviewed, represent the current state of the art in almost all instances. This book has much to argue for it and little to argue against it. It is clearly one of the better volumes on the topic and deserves the attention of the serious student of human sexuality.

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PRIMARY CARE GERIATRICS—A CASE-BASED LEARNING PROGRAM—Richard J. Ham, MD, Joseph H. Holtzman, PhD, Michelle L. Marcy, MS, and Marcia R. Smith, PhD; prepared under the auspices of the American Geriatrics Society. John Wright/PSG Inc., 545 Great Road, Littleton, MA 01460, 1983. 311 pages, $39.50 (softbound).

The in-depth study of geriatric medine by medical students, practicing physicians and other health professionals has been mandated by the changing demographic profile of our population. Medical schools and medical centers around the country are gradually awakening to this need and beginning to provide at least introductory courses in geriatrics. It is a field far more complex than many clinicians are aware. The dissection of normal aging from pathologic changes, the multiplicity and chronicity of diseases, the atypical presentations of disease, pharmacologic alterations in the aged, as well as the need for functional assessment in addition to standard differential diagnosis combine to make geriatric medicine a challenge to practitioners and teachers.

A variety of excellent geriatrics texts are available. All attempt in some way to show the need to depart from a standard organ systems approach when dealing with elderly patients. *Primary Care Geriatrics* represents an attempt to go further in synthesizing the physiology, medicine, sociology and psychology of aging. The format is a case-based programmed text, intended for medical students, house officers and other clinical health personnel. There are 15 chapters, or modules. The initial modules cover demography of aging, aging theory and physiology of aging. There is a module on techniques of evaluation, one on the health care system and community resources, a review of geriatric rehabilitation and finally eight modules that address specific common medical problems in elderly persons.

Each module begins with an overview of the topic to be discussed and a list of specific objectives. There is a short multiple choice pretest as well as a posttest for each module, with answers provided in an appendix. Illustrated case histories are used liberally to complement the text. The programmed text is a tool that appeals to some more than others. I found that it required considerable concentration to absorb information from the text and apply it to the case material. This was in part due to the presentation of portions of each case at different points in the text in order to illustrate specific features. For example, when historical clues to the etiology of confusion are discussed in the text, parts of the histories from several cases are presented. Additional history, physical findings and other data for each case are presented in segments throughout the remainder of the text. I found this fragmentation of the cases to be a bit disorienting, and I often had to return to earlier portions of the case presentation in order to piece together the whole. The pretests and posttests suffer from the usual simplistic approach of multiple choice instruments but do serve to focus on the specified objectives.

Overall, the material is quite comprehensive and I commend the authors for including subjects often omitted even in geriatric texts: the excellent introduction to rehabilitation, the consideration of the health care system and financing mechanisms as they apply to the elderly, a consideration of sexual dysfunction. References are extensive and largely up to date. Suggested readings are nicely divided into categories—for example, journal articles, books and monographs. A list of pertinent audiovisual materials will be of use to the instructor.

The text offers something at several levels. There is some material that is quite basic, while the later modules will be best utilized by those already having some clinical experience. Due to the time and concentration required by the format, this is not a book to be casually perused as a brief introduction to geriatric medicine. It will be best used by a student or clinician wishing to undertake an unhurried, serious first study of geriatrics.

LISA HEIKOFF, MD
Fellow in Geriatric Medicine
Mount Zion Hospital and Medical Center
San Francisco

* * *

CHOOSING EFFECTIVE LABORATORY TESTS—Carl E. Speicher, MD, Professor of Pathology, College of Medicine, and Director of Clinical Laboratories, University Hospitals, and Jack W. Smith, Jr, MD, MS, Instructor of Pathology, College of Medicine, and Associate Director of Clinical Chemistry, University Hospitals, The Ohio State University, Columbus, Ohio. W. B. Saunders Co., West Washington Square, Philadelphia, PA 19105, 1983. 375 pages, $45.00.

This medium-sized hardback is an excellent addition to the bookshelves of both practicing clinicians and those who are learning the concepts of clinical problem-solving strategies. Divided into three parts—concepts, clinical strategies and menus of unexplained laboratory results—the text is well organized and interlaced with substantive and appropriate tables and figures from common references.

The first section is entitled "Rationale and Useful Concepts." Drs Speicher and Smith presume we have read Galen and Gambino's *Beyond Normality* and understood the statistical and clinical uses of Bayes' theorem. Sensitivity (percentage of true positives in patients with disease) and specificity (percentage of true negatives in patients without disease) form the cornerstones of the strategies, with prevalence further conditioning the predictive values.

The reference to experienced clinicians using the "rifle approach" to utilization of clinical laboratory testing versus medical students and house officers shooting the laboratory "shotgun" has been lost on neither practicing pathologists (including those of us in academic medicine) nor federal, state and insurance company health care policymakers.

The authors remind us that real patients present as diagnostic dilemmas and thereby provide physicians the joy of discovering etiology and pathogenesis while traditional medical education and textbooks utilize the pathogenetic reasoning approach which presumes that the diagnosis is already known.

The problem-solving method uses diagnostic hypotheses as trial goals to satisfy, exclude or search for more information. Data must be authenticated regarding reliability and accuracy. Then hypotheses are triggered and evaluated. The authors review monopathic/simple/parsimonious *versus* polypathic/coincidental/multiple disease explanations and discuss "diagnosis at a glance," "spiraling pursuit" and experience-built decision trees. They suggest that we use laboratory tests to discriminate between rival hypotheses.

Using the presence or absence of pregnancy and diabetes mellitus, we are escorted through Bayes' rule toward predictive values. Computer-based "chaining" is explained and several examples of software packages for cognitive hypothesis-driven reasoning models related to diagnosis (occasionally to therapy) are given.

Concepts of turnaround time, interpretability, intralaboratory errors, critical values, communication, interpretive reports, STAT lab, specimen collection and handling are introduced.

Targeted *versus* multiphasic screening is reviewed. The discussion on unexpected test results reminds us that many "clinicians have simply learned to ignore data that do not fit with their clinical impressions" and that the pathologist is there "to

bridge the gap between laboratory technology and patient care more effectively." We are given a logical and practical sequential approach to reveal whether or not unexplained abnormalities are indicative of disease.

By starting with a suspected diagnosis derived from a history and physical examination and then formulating test strategies, the middle third of this book, "Clinical Subproblems," covers the contexts, strategies and interpretations of a series of real clinical problems. They range from acute myocardial infarction and the enzymes and isoenzymes of creatine kinase and lactic dehydrogenase to Wilson's disease and copper and ceruloplasmin determinations. This part of the book is not meant to be all inclusive but rather to show how the problem-solving, predictive and interpretive methodologies can be utilized on diagnostic and therapeutic issues in pragmatic terms. The authors advocate evaluation of all *curable* causes of hypertension rather than *all* patients with hypertension, for example. Suggestions about *not* performing tests are intermixed with the more obvious schemes concerning when to order tests.

A quotable quote appears in the endocrine chapter: "To avoid misinterpretations, the laboratory values should always be interpreted in the context of the clinical picture." Philosophies concerning laboratory utilization, cost effectiveness and decision analysis are thus related to genuine problems of clinical management. This section borrows heavily from Henry and Howanitz' treatise on organ panels in Jones and Palulonis' *Laboratory Tests in Medical Practice* (Chicago, AMA, 1980). Some omissions—such as respiratory problems in infants, in the "Pink Puffers vs. Blue Bloaters" section, or pancreatic pseudocysts in the role of pancreatic problems—are probably inevitable in a condensed series of examples, and a few errors may be found (*two* Tables 5-4 on page 63, "amylase-creatine" rather than "amylase-creatinine" ratio on page 234).

In part three, "Unexpected Test Results," omission of important and frequently ordered procedures such as direct bilirubin, prothrombin and partial thromboplastin times, pregnancy tests and urinalysis leaves us wondering why these were not listed in the excellent tables of 22 common laboratory tests. We might further wish that data on predictive values for many more tests were available in the general literature (this is no fault of the authors).

A high percentage of references are recent (less than five or six years old).

In summary, this book is highly recommended reading for strategists and teachers, as well as reference material for clinicians, pathologists and residents studying for board examinations. And, particularly in light of recent Medicare regulations, the authors leave us with a timely statement: "To implement effective strategies for problem solving . . . use a laboratory-based consultant."

THOMAS S. McCONNELL, MD
Director, Clinical Laboratories
Chief, Pathology Service
University of New Mexico Hospital
Albuquerque

* * *

POSTGRADUATE TEXTBOOK OF CLINICAL ORTHOPAEDICS—Edited by Nigel H. Harris, MA, FRCS, Consultant Orthopaedic Surgeon, St Mary's Hospital, London. John Wright • PSG Inc., 545 Great Rd., Littleton, MA 01460, 1983. 1,010 pages, $120.00.

This book is a 1,000-page, multiauthored comprehensive review of the current "state of the art" in orthopedic surgery, 1983. A majority of the authors of this book are from the United Kingdom with a few from the United States. This book stresses the description, etiology and evaluation of musculoskeletal conditions. Treatment, and especially surgical techniques, are given relatively little coverage although these areas are given more attention in the sections on rheumatoid disease and joint replacement. Pediatric orthopedics and rheumatoid disease are dealt with more extensively than other subjects. Trauma and fracture care are not covered in this textbook.

The strength of this book is its relatively broad coverage of orthopedics which, though it limits its depth, allows the student of orthopedics a quick review of most subjects. Certain chapters, especially those on the pediatric spine and neuromuscular diseases, have excellent recent bibliographies. This allows for a more detailed study of the subject in question if desired. Because the book's authors primarily are British, American readers will become more knowledgeable about the practice of orthopedics in the United Kingdom, which can be quite different from that in the United States. Awareness of these differences will broaden the orthopedic knowledge of the reader.

The weakness of this book is related to its size, which allows for a relatively superficial coverage of many areas. Orthopedic knowledge is expanding dramatically, and the resident and practicing orthopedic surgeon generally need more in-depth knowledge of an individual subject than this book provides. In a book of this type, access to more detailed information should be provided by a comprehensive up-to-date bibliography. In many chapters, the references are dated and sparse. In particular, the bibliographies in chapters on the lumbar spine, cervical spine, shoulder, hand and slipped capital epiphysis are particularly weak. Certain chapters in this book have an author bias and, thus, are not really a fair overview of the subject. This could be a problem for a beginning orthopedist who might not be able to detect this and, therefore, could come away with a skewed view of the subject.

In summary, this book is recommended for American orthopedists who wish a current perspective of British orthopedics. For these readers, in many areas additional knowledge will be necessary and monographs or journal articles will need to be consulted. The book is probably most valuable for medical students and beginning orthopedics residents who need a quick introduction to an orthopedic entity.

RONALD J. KENDIG, MD
Sacramento, California

* * *

HANDBOOK OF OBSTETRICS & GYNECOLOGY—Eighth Edition—Ralph C. Benson, MD, Professor and Chairman Emeritus, Department of Obstetrics and Gynecology, Oregon Health Sciences University, Portland; illustrated by Laurel V. Schaubert. Lange Medical Publications, Drawer L, Los Altos, CA 94022, 1983. 804 pages, $13.00 (softbound).

The eighth edition of Benson's *Handbook of Obstetrics and Gynecology* is a continuation of the excellent work presented in the earlier editions. It is a concise synopsis of the major areas of the field and is presented in a simple, easy-to-read fashion.

A major drawback for all concise presentations is the necessity to present only the basic issue in a simplistic fashion. This is true in this edition also. As a result, the book is best suited for the beginning student of obstetrics and gynecology and for the occasional practitioner of the specialty. It will also be helpful as a reference for non-ob-gyn physicians who seek to review the treatment recommended for conditions of females but do not wish to read about multiple or controversial ideas.

RALPH W. HALE, MD
Professor and Chairman
Department of Obstetrics-Gynecology
University of Hawaii
John A. Burns School of Medicine
Honolulu

* * *

COMPUTERIZING YOUR MEDICAL OFFICE: A GUIDE FOR PHYSICIANS AND THEIR STAFFS—Dot Sellers, CMA-A. Medical Economics Books, Oradell, NJ 07649, 1983. 213 pages, $17.50 (paperback).

This book does an excellent job of approaching the subject of the current capabilities of medical office computing systems. In a well-organized, comprehensible fashion, the author discusses each phase of computer acquisition and use from consideration of whether to computerize to computer upkeep. The considerations are stated with sufficient specificity to be practical but with sufficient generality to be durable in a rapidly changing field. It is likely that the price ranges quoted will be inaccurate long before anything else is.

I would recommend this book to any physician or office manager who has asked the question "Could a computer help me?" but who does not yet possess the perfect system.

ROGER K. HOWE, MD
Mt. Shasta, California

(Continued from Page 194)

OF INTEREST TO ALL PHYSICIANS

February 22-23—**American College of Physicians: 1985 Regional Scientific CME Meeting.** ACP at Doubletree Inn, Monterey. Friday-Saturday. Contact: Jerry P. Lewis, MD, 618 Francisco Place, Davis 95616.

February 23-24—**Expanding Horizons.** UCSF at Golden Gateway Holiday Inn, San Francisco. Saturday-Sunday. Contact: UCSF.

February 28-March 2—**California Medical Association Postgraduate Institute.** Curry Village, Yosemite. Thursday-Saturday. Contact: CMA, 44 Gough St., San Francisco 94103-1233. (415) 863-5522.

March 1—**11th Annual Diabetes Program.** UCD. Friday.

March 2-3—**San Francisco Academy of Hypnosis Annual Workshop** at Letterman Army Medical Center, San Francisco. Saturday-Sunday. 28 hrs. Fee: $300. Contact: Jan Brooks, SFAH, 2820 15th Ave., San Francisco, CA 94114.

March 3-6—**Maxillofacial Trauma.** UCSF at Hyatt Lake Tahoe, Incline Village. Sunday-Wednesday.

March 6-8—**35th Annual Course for Physicians in Family Practice.** Mount Zion Hospital and Medical Center, San Francisco. Wednesday-Friday. Contact: Robin Jackson, Office of Continuing Education, PO Box 7921, San Francisco 94115. (415) 885-7269.

March 7-10—**Dermatologic Survey: State of the Art.** UCSF at Incline Village, Nevada. Thursday-Sunday. Fee: $400.

March 8-13—**California Medical Association Annual Session** at Town and Country Hotel, San Diego. Friday-Wednesday. Contact: Barbara Smart, CMA, 44 Gough St., San Francisco 94103-1233. (415) 863-5522, ext. 404.

March 10-13—**New Strategies for Common Clinical Problems.** UCSF at Granlibakken Ski and Raquet Resort, Tahoe City. Sunday-Wednesday.

March 13-17—**Orthopaedic Symposium.** UCD at Silverado Country Club, Napa. Wednesday-Sunday.

March 14-16—**New Approaches to the Diagnosis and Treatment of Diseases of the Elderly.** Annenberg Center for Health Science. Thursday-Saturday. Contact: Annenberg Center for Health Science, Eisenhower Medical Center, 39000 Bob Hope Dr., Rancho Mirage 92270.

March 15-23—**Reider Laser Center Symposium.** UCI. One week.

March 20-22—**Advances and Controversies in Bronchial Asthma.** California Thoracic Society at Marriott's Santa Barbara Biltmore Hotel, Santa Barbara. Wednesday-Friday. Contact: Medical Education Director, California Thoracic Society, 424 Pendleton Way, Oakland 94621. (415) 638-5864.

March 21-22—**Current Practices in Diagnosis & Treatment of Arthritis—Connective Tissues and Musculoskeletal Diseases.** Palo Alto Medical Foundation at St. Francis Hotel, San Francisco. Thursday-Friday. 12 hrs. Contact: Palo Alto Medical Foundation, 385 Homer Ave, Palo Alto, 94301.

March 22-23—**Cancer and Sexuality Postgraduate Institute.** California Medical Association at Marriott Inn, Marina del Rey. Friday-Saturday. Contact: CMA, 44 Gough St, San Francisco 94103-1233. (415) 863-5522.

March 25-29—**Family Practice Refresher Course—1985.** UCSD at Palm Springs Spa Hotel. Monday-Friday. 30 hrs.

March 29-31—**Office Emergencies in Primary Care.** Continuing Medical Education Associates at Hotel Del Coronado, San Diego. Friday-Sunday. 18 hrs. Fee: $275. Contact: Jackie Shiller, CMEA, PO Box 84296, San Diego 92138. (619) 223-2997.

April 8-11—**Diabetes Mellitus: Modern Management Methods.** LLU at Maui Marriott, Maui. Monday-Wednesday. 16 hrs.

April 12-17—**2nd Annual Spring Conference.** Western Regional Chapters of the Society of Nuclear Medicine at Hotel Intercontinental, San Diego. Friday-Wednesday. 25 hrs. Contact: Justine Parker, PO Box 40279, San Francisco 94140. (415) 647-0722.

April 17-21—**Mountain Medicine: 1985.** UCD at North Lake Tahoe. Wednesday-Sunday.

April 24-28—**Annual Scientific Program and Postgraduate Course.** Pacific Coast Fertility Society at Caesars Palace, Las Vegas. Wednesday-Sunday. 23 hrs. Contact: Pacific Coast Fertility Society, 5820 Wilshire Blvd., #500, Los Angeles 90036. (213) 937-5514.

April 27-28—**13th Annual Family Practice Symposium.** Southern Permanente Group at Disneyland Hotel, Anaheim. Friday-Saturday. 11 hrs. Contact: Southern California Kaiser Permanente Group, 4747 Sunset Blvd, Los Angeles 90027.

May 3—**One Day Orthopaedics and Casting Procedures Workshop.** Continuing Medical Education Associates at Holiday Inn, Union Square, San Francisco. Friday. 7 hrs. Fee: $165. Contact: J. Shiller, CME Assoc., PO Box 84296, San Diego 92138. (619) 223-2997.

May 5—**One Day Orthopaedics and Casting Procedures Workshop.** Continuing Medical Education Associates at Grand Hotel, Anaheim. Sunday. 7 hrs. Fee: $165. Contact: J. Shiller, CME Assoc., PO Box 84296, San Diego 92138. (619) 223-2997.

(Continued on Page 280)

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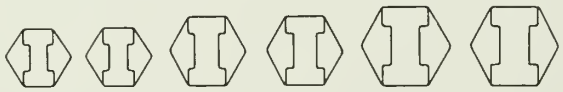

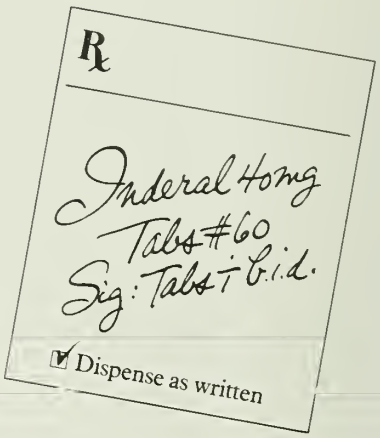

BRIEF SUMMARY (FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE CIRCULAR.)

INDERAL® (propranolol hydrochloride) Tablets

CONTRAINDICATIONS

INDERAL is contraindicated in 1) cardiogenic shock, 2) sinus bradycardia and greater than first degree block, 3) bronchial asthma, 4) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL.

WARNINGS

CARDIAC FAILURE: Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta blockade may precipitate more severe failure. Although beta blockers should be avoided in overt congestive heart failure, if necessary they can be used with close follow-up in patients with a history of failure who are well compensated and are receiving digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle.

IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta blockers can, in some cases, lead to cardiac failure. Therefore, at the first sign or symptom of heart failure, the patient should be digitalized and/or treated with diuretics, and the response observed closely; or INDERAL should be discontinued (gradually, if possible).

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following abrupt discontinuance of INDERAL therapy. Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced over at least a few weeks and the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema) – PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

MAJOR SURGERY: The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

INDERAL, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in starting and maintaining the heartbeat has also been reported with beta blockers.

DIABETES AND HYPOGLYCEMIA: Beta-adrenergic blockade may prevent the appearance of certain premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia in labile insulin-dependent diabetes. In these patients, it may be more difficult to adjust the dosage of insulin.

THYROTOXICOSIS: Beta blockade may mask certain clinical signs of hyperthyroidism. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

PRECAUTIONS

General: Propranolol should be used with caution in patients with impaired hepatic or renal function. INDERAL is not indicated for the treatment of hypertensive emergencies.

Beta-adrenoreceptor blockade can cause reduction of intraocular pressure. Patients should be told that INDERAL (propranolol hydrochloride) may interfere with the glaucoma screening test. Withdrawal may lead to a return of increased intraocular pressure.

Clinical Laboratory Tests: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

DRUG INTERACTIONS: Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if INDERAL is administered. The added catecholamine-blocking action may produce an excessive reduction of resting sympathetic nervous activity which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In 18-month studies in both rats and mice, employing doses up to 150 mg/kg/day, there was no evidence of significant drug-induced toxicity. There were no drug-related tumorigenic effects at any of the dosage levels. Reproductive studies in animals did not show any impairment of fertility that was attributable to the drug.

Pregnancy: Pregnancy Category C. INDERAL has been shown to be embryotoxic in animal studies at doses about 10 times greater than the maximum recommended human dose.

There are no adequate and well-controlled studies in pregnant women. INDERAL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: INDERAL is excreted in human milk. Caution should be exercised when INDERAL is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Most adverse effects have been mild and transient and have rarely required the withdrawal of therapy.

Cardiovascular: bradycardia; congestive heart failure, intensification of AV block, hypotension, paresthesia of hands, thrombocytopenic purpura, arterial insufficiency, usually of the Raynaud type.

Central Nervous System: Lightheadedness, mental depression manifested by insomnia, lassitude, weakness, fatigue, reversible mental depression progressing to catatonia; visual disturbances, hallucinations, an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Gastrointestinal: nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis.

Allergic: pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Respiratory: bronchospasm.

Hematologic: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Auto-Immune: In extremely rare instances, systemic lupus erythematosus has been reported.

Miscellaneous: alopecia, LE-like reactions, psoriasiform rashes, dry eyes, male impotence, and Peyronie's disease have been reported rarely. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been associated with propranolol.

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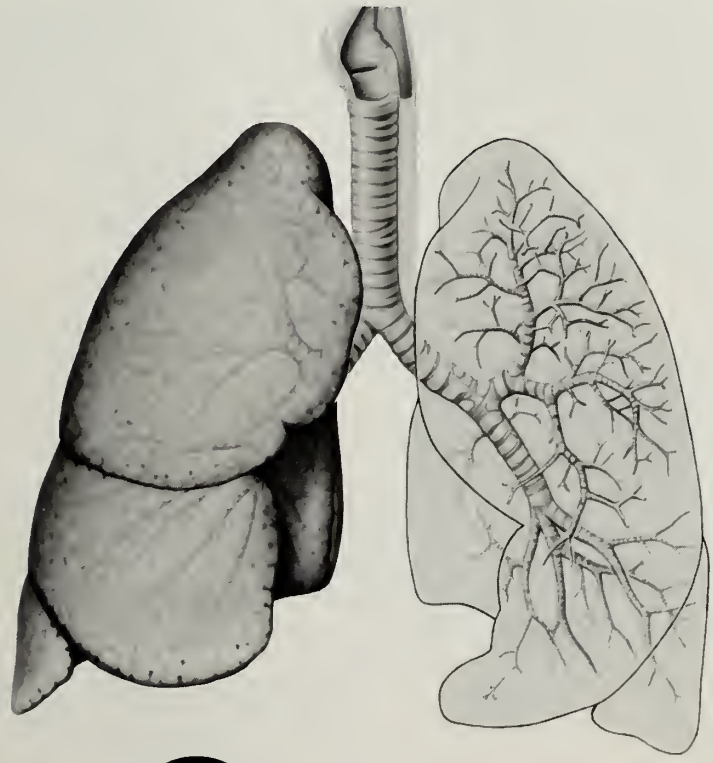
Consider the causative organisms...



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(ampicillin-susceptible) (ampicillin-resistant)

Brief Summary: Consult the package literature for prescribing information.

Indications and Usage: Ceclor* (cefaclor, Lilly) is indicated in the treatment of the following infections when caused by susceptible strains of the designated microorganisms

Lower respiratory infections, including pneumonia caused by *Streptococcus pneumoniae* (*Diplococcus pneumoniae*), *Haemophilus influenzae*, and *S. pyogenes* (group A beta-hemolytic streptococci)

Appropriate culture and susceptibility studies should be performed to determine susceptibility of the causative organism to Ceclor.

Contraindication: Ceclor is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

Warnings: IN PENICILLIN-SENSITIVE PATIENTS, CEPHALOSPORIN ANTIBIOTICS SHOULD BE ADMINISTERED CAUTIOUSLY THERE IS CLINICAL AND LABORATORY EVIDENCE OF PARTIAL CROSS-ALLERGENICITY OF THE PENICILLINS AND THE CEPHALOSPORINS, AND THERE ARE INSTANCES IN WHICH PATIENTS HAVE HAD REACTIONS, INCLUDING ANAPHYLAXIS, TO BOTH DRUG CLASSES.

Antibiotics, including Ceclor, should be administered cautiously to any patient who has demonstrated some form of allergy, particularly to drugs.

Pseudomembranous colitis has been reported with virtually all broad-spectrum antibiotics (including macrolides, semisynthetic penicillins, and cephalosporins); therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with the use of antibiotics. Such colitis may range in severity from mild to life-threatening.

Treatment with broad-spectrum antibiotics alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis.

Mild cases of pseudomembranous colitis usually respond to drug discontinuance alone. In moderate to severe cases, management should include sigmoidoscopy, appropriate bacteriologic studies, and fluid, electrolyte, and protein supplementation. When the colitis does not improve after the drug has been discontinued, or when it is severe, oral vancomycin is the drug of choice for antibiotic-associated pseudomembranous colitis produced by *C. difficile*. Other causes of colitis should be ruled out.

Precautions: *General Precautions* — If an allergic reaction to Ceclor* (cefaclor, Lilly) occurs, the drug should be discontinued, and, if necessary, the patient should be treated with appropriate agents, *e.g.*, pressor amines, antihistamines, or corticosteroids.

Prolonged use of Ceclor may result in the overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Positive direct Coombs' tests have been reported during treatment with the cephalosporin antibiotics. In hematologic studies or in transfusion cross-matching procedures when antiglobulin tests are performed on the minor side or in Coombs' testing of newborns whose mothers have received cephalosporin antibiotics before parturition, it should be recognized that a positive Coombs' test may be due to the drug.

Ceclor should be administered with caution in the presence of markedly impaired renal function. Under such conditions, careful clinical observation and laboratory studies should be made because safe dosage may be lower than that usually recommended.

As a result of administration of Ceclor, a false-positive reaction for glucose in the urine may occur. This has been observed with Benedict's and Fehling's solutions and also with Clinitest® tablets but not with Tes-Tape® (Glucose Enzymatic Test Strip, USP, Lilly).

Broad-spectrum antibiotics should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.

Usage in Pregnancy — *Pregnancy Category B* — Reproduction studies have been performed in mice and rats at doses up to 12 times the human dose and in ferrets given three times the maximum human dose and have revealed no evidence of impaired fertility or harm to the fetus due to Ceclor* (cefaclor, Lilly). There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers — Small amounts of Ceclor have been detected in mother's milk following administration of single 500-mg doses. Average levels were 0.18, 0.2D, 0.21, and 0.16 mcg/ml at two, three, four, and five hours respectively. Trace amounts were detected at one hour. The effect on nursing infants is not known. Caution should be exercised when Ceclor is administered to a nursing woman.

Usage in Children — Safety and effectiveness of this product for use in infants less than one month of age have not been established.

Adverse Reactions: Adverse effects considered related to therapy with Ceclor are uncommon and are listed below.

Gastrointestinal symptoms occur in about 2.5 percent of patients and include diarrhea (1 in 70).

Symptoms of pseudomembranous colitis may appear either during or after antibiotic treatment. Nausea and vomiting have been reported rarely.

Hypersensitivity reactions have been reported in about 1.5 percent of patients and include morbiliform eruptions (1 in 100). Pruritus, urticaria, and positive Coombs' tests each occur in less than 1 in 200 patients. Cases of serum-sickness-like reactions (erythema multiforme or the above skin manifestations accompanied by arthritis/arthralgia and, frequently, fever) have been reported. These reactions are apparently due to hypersensitivity and have usually occurred during or following a second course of therapy with Ceclor. Such reactions have been reported more frequently in children than in adults. Signs and symptoms usually occur a few days after initiation of therapy and subside within a few days after cessation of therapy. No serious sequelae have been reported. Antihistamines and corticosteroids appear to enhance resolution of the syndrome.

Cases of anaphylaxis have been reported, half of which have occurred in patients with a history of penicillin allergy.

Other effects considered related to therapy included eosinophilia (1 in 50 patients) and genital pruritus or vaginitis (less than 1 in 100 patients).

Causal Relationship Uncertain — Transitory abnormalities in clinical laboratory test results have been reported. Although they were of uncertain etiology, they are listed below to serve as alerting information for the physician.

Hepatic — Slight elevations in SGOT, SGPT, or alkaline phosphatase values (1 in 40).

Hematopoietic — Transient fluctuations in leukocyte count, predominantly lymphocytosis occurring in infants and young children (1 in 40).

Renal — Slight elevations in BUN or serum creatinine (less than 1 in 500) or abnormal urinalysis (less than 1 in 200).

[0617B2R]

Note: Ceclor* (cefaclor, Lilly) is contraindicated in patients with known allergy to the cephalosporins and should be given cautiously to penicillin-allergic patients.

Penicillin is the usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. See prescribing information.

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Lilly

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Additional information available to the profession on request from Eli Lilly and Company Indianapolis, Indiana 46285

Eli Lilly Industries, Inc
Carolina, Puerto Rico 0063D

(Continued from Page 276)

May 11-17—**San Francisco Orthopaedic Review—1985.** UCSF at Golden Gateway Holiday Inn, San Francisco. Tuesday-Sunday. 41 hrs.

May 15-17—**Child Abuse: Systems of Intervention.** UCD at Holiday Inn Holidome, Sacramento. Friday-Sunday.

May 19-23—**Current Concepts in Primary Care: 12th Annual Family Practice Refresher Course.** UCD at Napa Valley. Sunday-Thursday.

ALASKA

June 8-11—**Alaska State Medical Association—Annual Meeting.** Haines. Saturday-Tuesday. Contact: ASMA, 4107 Laurel St., Anchorage 99504. (907) 562-2662.

IDAHO

February 16-23—**Internal Medicine.** University of Washington School of Medicine at Elkhorn Resort, Sun Valley. One week. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

February 17-22—**11th Stanford-Palo Alto Medical Foundation Research Institute Winter Course in Infectious Diseases.** Sun Valley. Sunday-Friday. Contact: Registrar, American College of Physicians, 4200 Pine St., Philadelphia, PA 19104.

February 23-March 2—**Office Orthopaedics.** University of Washington School of Medicine at Elkhorn Resort, Sun Valley. One week. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

March 1-3—**Winter Clinic—Sports Medicine.** Shore Lodge-Brundage Mountain for "Great Alpine-Powder Skiing," McCall. Friday-Sunday. Contact: Ada County Medical Society, PO Box 2668, Boise 83701. (208) 336-2930.

March 2-9—**Electromyography.** University of Washington School of Medicine at Elkhorn Resort, Sun Valley. One week. Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

MONTANA

February 20-23—**Big Sky Pulmonary/Ski Conference.** American Lung Association of Montana at Big Sky of Montana. Wednesday-Saturday. Contact: ALA of Montana, 825 Helena Ave., Helena 59601. (406) 442-6556.

NEW MEXICO

Information, requests for accreditation and items to be listed should be sent to the chairman of the CME Committee, New Mexico Medical Society, 303 San Mateo NE, Suite 204, Albuquerque, NM 87108 at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 266-7868.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

February 15-16—**Heal Thyself—A Seminar Focusing on Quality of Life and Caring for Others.** Albuquerque. Friday-Saturday. Clarion Four Seasons. 11 hrs. AMA Cat. I. Contact: Office of CME, Presbyterian Hospital, Albuquerque 87102. (505) 841-1225.

February 21-23—**18th Annual OB/GYN Postgraduate Seminar.** Albuquerque. Thursday-Saturday. AMFAC Hotel. 15 hrs. AMA Cat. I. Contact: Office of CME, UNM SOM, Albuquerque 87131. (505) 277-3942.

February 22-24—**13th Annual Taos Lung Disease Symposium.** Taos. Friday-Sunday. Kachina Lodge. 12 hrs. AMA Cat. 1. Contact: New Mexico Chapter, American Thoracic Society, 216 Truman NE, Albuquerque 87108. (505) 265-0732.

February 28-March 2—**First Ruidoso Heart Seminar—Practical Cardiology.** Ruidoso. Thursday-Saturday. Inn of the Mountain Gods. Contact: NM Heart Association, 2403 San Mateo NE, Albuquerque 87108. (505) 268-3711.

March 8-10—**Arthritis Foundation Symposium and Harris Galante Hip Replacement Workshop.** Albuquerque. Friday-Sunday. AMFAC Hotel. Contact: The Arthritis Foundation, 5112 Grand Avenue NE, Albuquerque 87106. (505) 265-1545.

(Continued on Page 282)

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See brief summary of prescribing information on next page.

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It is contraindicated in all children with fever accompanied by dehydration. ▫ **WARNINGS**: ZORprin® should be used with caution when anticoagulants are prescribed concurrently, since aspirin may depress the concentration of prothrombin in plasma and increase bleeding time. Large doses of salicylates may have hypoglycemic action and enhance the effect of the oral hypoglycemics, concomitant use therefore is not recommended. However, if such use is necessary, dosage of the hypoglycemic agent must be reduced. The hypoglycemic action of the salicylates may also necessitate adjustment of the insulin requirements of diabetics. While salicylates in large doses have a uricosuric effect, smaller amounts may reduce the uricosuric effect of uricosuric agents. ▫ **USE IN PREGNANCY**: Aspirin can cause fetal harm when administered to pregnant women. Aspirin interferes with maternal and infant blood clotting and may lengthen the duration of pregnancy and parturition. Aspirin has produced teratogenic effects and increases the incidence of stillbirths and neonatal deaths in animals. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Aspirin should not be taken during the last 3 months of pregnancy. ▫ **PRECAUTIONS**: Appropriate precautions should be taken in prescribing ZORprin® for patients who are known to be sensitive to aspirin or salicylates. Particular care should be used when prescribing this medication for patients with erosive gastritis, peptic ulcer, mild diabetes or gout. As with all salicylate drugs, caution should be exercised in prescribing ZORprin® for those patients with bleeding tendencies or those on anticoagulant drugs. Large doses of salicylates should be avoided in patients with clear evidence of carditis. In order to avoid exacerbation of disease or adrenal insufficiency, patients who have been on prolonged corticosteroid therapy should have their therapy tapered slowly rather than discontinued abruptly when ZORprin® (aspirin) is made a part of the treatment program. Patients receiving large doses of aspirin and/or prolonged therapy may develop mild salicylate intoxication (salicylism) that may be reversed by reduction in dosage. Salicylates can produce changes in thyroid function tests. Salicylates should be used with caution in patients with severe hepatic damage, preexisting hypoprothrombinemia, Vitamin K deficiency and in those undergoing surgery. Since aspirin release from ZORprin® is pH dependent, it may change in those conditions where the gastric pH has been increased via antacids, gastric secretion inhibitors or surgical procedures. ▫ **ADVERSE REACTIONS**: **Hematologic**: Aspirin interferes with blood clotting. Patients with a history of blood coagulation defects or receiving anti-coagulant drugs or with severe anemia should avoid ZORprin®. Aspirin used chronically may cause a persistent iron deficiency anemia. **Gastrointestinal**: Aspirin may potentiate peptic ulcer, and cause stomach distress or heartburn. Aspirin can cause an increase in occult bleeding and in some patients massive gastrointestinal bleeding. However, the greatest release of active drug from ZORprin® is designed to occur in the small intestine over a period of time. This has resulted in less symptomatic gastrointestinal side effects. **Allergic**: Allergic and anaphylactic reactions have been noted when hypersensitive individuals have taken aspirin. The most common allergic reaction to aspirin is the induction of bronchospasm with asthma-like symptoms. Other reactions are hives, rash, angioedema, as well as rhinitis and nasal polyps. Fatal anaphylactic shock, while not common, has been reported. **Central Nervous System**: Taken in overdoses, aspirin provides stimulation which may be manifested by tinnitus. Following initial stimulation, depression of the central nervous system may be noted. **Renal**: Aspirin may rarely cause an increase in the severity of chronic kidney disease. **Hepatic**: High doses of aspirin have been reported to produce reversible hepatic dysfunction. ▫ **OVERDOSAGE**: Overdosage, if it occurs, would produce the usual symptoms of salicylism, tinnitus, vertigo, headache, confusion, drowsiness, sweating, hyperventilation, vomiting or diarrhea. Treatment for mild intoxication, emptying the stomach with an emetic, or gastric lavage with 5% sodium bicarbonate. Individuals suffering from severe intoxication should, in addition, have forced diuresis by intravenous infusions of saline and sodium bicarbonate or sodium lactate, dextrose solution. In extreme cases, hemodialysis or peritoneal dialysis may be required. ▫ **HOW SUPPLIED**: ZORprin® tablets 800 mg, plain, white capsule-shaped tablets. Bottles of 100 tablets. ▫ **CAUTION**: Federal Law prohibits dispensing without prescription. Manufactured and distributed by: Boots Pharmaceuticals, Inc. Shreveport, LA, 71106 USA

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CONTINUING MEDICAL EDUCATION

(Continued from Page 280)

March 15-16—**Primary Care Orthopaedics.** Albuquerque. Friday-Saturday. AMFAC Hotel. 15 hrs. AMA Cat. I. Contact: Office of CME, UNM SOM, Albuquerque 87131. (505) 277-3942.

April 11-13—**Seventh Annual Pediatric Cardio-Pulmonary Update.** Thursday-Saturday. AMFAC Hotel. 15 hrs. AMA Cat. I. Contact: Office of CME, UNM SOM, Albuquerque 87131. (505) 277-3942.

OREGON

The following list of continuing medical offerings in the state of Oregon is compiled by the Oregon Medical Association's Council on Medical Education. If you wish to submit information regarding future postgraduate courses, please submit the information to James A. Kronenberg, Associate Executive Director, Oregon Medical Association, 5210 SW Corbett Ave., Portland, OR 97201, or phone (503) 226-1555.

MEDICAL GRAND ROUNDS

Douglas Community Hospital, 738 West Harvard Avenue, Roseburg 97470:

Every Monday, 12:30 p.m. Contact: Robert A. Driver, MD, Douglas Community Hospital, 738 West Harvard Avenue, Roseburg, OR 97470. (503) 673-6641.

Emanuel Hospital, 2801 N. Gantenbein Street, Portland 97227:

Every Friday, 8:00 a.m. to 9:00 a.m. **Medical Grand Rounds.** Contact: Philipa McClure, Emanuel Hospital, 2801 N. Gantenbein Street, Portland, OR 92227. (505) 280-3200.

Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland 97210:

Every Wednesday, 8:00 a.m. to 9:00 a.m. **Medicine Grand Rounds.** Nursing Education Building, Room 110. Contact: Department of Medicine, Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland, OR 97201. (503) 229-7454.

CONTACT INFORMATION

OHSU-CME—Contact: Division of Continuing Medical Education, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8700.

(Continued on Page 284)

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CONTINUING MEDICAL EDUCATION

(Continued from Page 282)

Providence Medical Center, 4805 NE Glisan, Portland 97213:

Every Wednesday, 8:00 a.m. **Medical Grand Rounds.** Contact: Richard Wernick, MD, Providence Medical Center, 4805 NE Glisan, Portland, OR 97213. (503) 230-6085.

Sacred Heart General Hospital, 1200 Alder Street, Eugene, OR 97440:

Every Tuesday, 8:00 a.m. to 9:00 a.m. **Medical Grand Rounds.** Hospital Auditorium. Contact: Medical Education Committee. PO Box 10905, Eugene, OR 97440.

Salem Hospital, 665 Winter Street SE, Salem 97301:

First and third Thursday of each month 7:15 a.m. to 8:15 a.m. **Medical Live Audit Conference.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter Street SE, Salem, OR 97301. (503) 370-5339.

Every Friday, 7:30 a.m. to 8:30 a.m. **Friday Grand Rounds.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter Street SE, Salem, OR 97301. (503) 370-5339.

St. Vincent Hospital & Medical Center, 9205 SW Barnes Road, Portland 97225:

First, third, fourth and fifth Wednesday of each month, 8:00 a.m. to 9:00 a.m. **Medical Grand Rounds.** Souther Auditorium. Contact: Bonnie Conger, Secretary to Dr Kenneth Melvin, St. Vincent Hospital & Medical Center, 9205 SW Barnes Road, Portland 97225. (503) 297-4411, Ext. 2230

Oregon Health Sciences University, Department of Psychiatry, Portland 97201:

Every Wednesday, 4:00 p.m. to 5:00 p.m. **Department of Psychiatry Grand Round Presentations.** Room 8B-60, University Hospital South, Oregon Health Sciences University. Contact: Dept. of Psychiatry, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8144.

(Continued on Page 285)

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CONTINUING MEDICAL EDUCATION

(Continued from Page 284)

Oregon Health Sciences University, Department of Medicine, Portland 97201:

Every Tuesday, 8:00 a.m. to 9:00 a.m. **Department of Medicine Grand Rounds.** U.H.S.-8B-60, Oregon Health Sciences University. Contact: Dept. of Medicine, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8607.

FAMILY PRACTICE GRAND ROUNDS

Every Wednesday, 11:00 a.m. to 12:00 Noon. **Family Practice Grand Rounds.** Family Practice Center, Oregon Health Sciences University, Portland. Contact: William A. Fisher, MD, Oregon Health Sciences University, Department of Family Practice, Portland, OR 97201. (503) 225-7590.

DERMATOLOGY

March 27-28—**Dermatopathology Conference.** Portland. Wednesday-Thursday. Marriott Hotel. Contact: OHSU-CME.

FAMILY PRACTICE

March 1-2—**Difficult Problems in Surgery.** Portland. Friday-Saturday. Red Lion Lloyd Center. Contact: OHSU-CME.

March 9—**Consultations in Gastroenterology Series.** Portland. Saturday. Marriott Hotel. Contact: OHSU-CME.

PATHOLOGY

March 27-28—**Dermatopathology Conference.** Portland. Wednesday-Thursday. Marriott Hotel. Contact: OHSU-CME.

SURGERY

March 1-2—**Difficult Problems in Surgery.** Portland. Friday-Saturday. Red Lion Lloyd Center. Contact: OHSU-CME.

OF INTEREST TO ALL PHYSICIANS

February 28-March 3—**Update in Rheumatology—1985.** Bend. Thursday-Sunday. Inn of the Seventh Mountain. Contact: OHSU-CME.

(Continued on Page 289)

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PHYSICIANS WANTED—California—Ventura County Group Practice seeks to employ BC/BE Family Physician to run satellite clinic. Opening scheduled for early 1985. Please contact Garrett Clifford, (805) 482-0773.

WASHINGTON, EMERGENCY PHYSICIAN: Immediate opening for board qualified physician in new community hospital in Olympia. Long established local physician group. Guaranteed minimum. Send CV to Mark Urmanski, MD, PO Box 2786, Olympia, WA 98507 or call Ray Brasher at (206) 456-7289

LIFE STYLE CHANGE! ARIZONA: Seeking full-time general surgeon, Board Certified, experienced. We have 217 general medical and surgical beds, 47 of which are surgical and 6 ICU. Prescott is located in the mountains of North Central Arizona, with a population of 25,000. Salary range is $70,000 to $80,000 depending upon qualifications. Send vitae to: F.C. Lepperd, Jr., MD, Chief of Staff, VA Medical Center, Prescott, AZ 86313, or call (602) 445-4860, ext. 301; Equal Opportunity Employer.

ALASKA: Family Practitioner, Board eligible/certified, to join the Fairbanks office of Alaska's largest multi-specialty clinic. Generous guaranteed salary, benefits, and relocation allowance. Partnership opportunity. Contact: Administrator, Fairbanks Clinic, 1867 Airport Rd, Fairbanks, AK 99701.

(Continued on Page 288)

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. . . YOU PROBABLY THOUGHT ABOUT THE PEOPLE YOU WOULD HELP.

If you would still like to pursue a career in medicine instead of business administration, you can have a quality practice with an excellent income in one of our well-equipped and modern acute care community hospitals in rural America. We'll take care of the annoyances of administration, finance, and government regulation while you take care of people.

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Los Angeles, CA 90067

(Continued from Page 286)

CALIFORNIA—Family Practice Director and experienced FP physicians sought for dynamic Central California single specialty group. Rapidly expanding practice offers attractive compensation, malpractice paid, and interaction with teaching faculty of the University of California, San Francisco's affiliate in Fresno. Send CV to: Brooke Newel, CCFMG/WJ, 1921 North Gateway Blvd., Fresno, CA 92727.

NORTHERN CALIFORNIA: Physician, Board certified/qualified in Emergency Medicine or Family Practice, to work part-time in a busy freestanding emergency center. Competitive compensation, malpractice, and bonus for part-time position. Full-time position will also include health insurance, vacation, educational expenses and other benefits. Send CV and references to Joanne Berkowitz, MD, The Emergency Center Medical Group, 4948 San Juan Avenue, Fair Oaks, CA 95628.

FAMILY PRACTICE—Excellent opportunity in New Mexico and Colorado communities for private practice with income quarantee. Send CV to Dave Templeton, Southwest Community Health Services, Albuquerque, NM 87102, or call 1 (800) 545-4030, extension 3050.

INTERNAL MEDICINE—Excellent opportunity in New Mexico and Colorado communities for private practice with income guarantee. Send CV to Dave Templeton, Southwest Community Health Services, Albuquerque, NM 87102, or call 1 (800) 545-4030, extension 3050.

ANTERIOR SEGMENT FELLOWSHIP in busy private practice associated with Medical College. Intraocular Lens Implantation, including posterior chamber and anterior chamber lenses. Extracapsular and Phacoemulsification techniques. Argon and Yag Laser. Excellent benefits plus fringes. Send CV and career objectives to: Box 6450, Western Journal of Medicine, 44 Gough St., San Francisco, CA 94103.

GENERAL/FAMILY PRACTITIONERS. If you are looking for an opportunity to be in the forefront of medical care, practice preventive medicine, work with other innovative professionals, and earn a comfortable living in pleasant surroundings, send your curriculum vitae to Physician Placement Dept-49. An equal opportunity employer. CIGNA Healthplans of California, 700 N. Brand Blvd., Suite 500, Glendale, CA 91203.

FAMILY PHYSICIANS—Two full-time, one half-time Board certified, residency trained Family Physicians to join six physician Family Practice dept. in 67 physician multispecialty clinic. One physician to fill Family Practice and Industrial Medicine position (industrial medicine experience, training or residency desirable). Other positions in main or satellite clinic with Family Medicine practice only. 100 bed community hospital next door with full lab, x-ray and subspecialty support (including CT scanner in clinic) available when needed. Write or call collect R. V. Sprinkle, MD, or R. H. Holland, MD, (916) 666-2466, 1207 Fairchild Ct., Woodland, CA 95695.

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We are a 148-bed JCAH acute hospital with satellite operations. We have openings for board certified and/or board eligible Surgeons in the following areas:

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GENERAL SURGEON—Opening in a young dynamic growing consultative practice. This 130-physician, multispecialty, prepaid group is located near Pacific Ocean beaches, Lake Tahoe ski areas, Stanford University and San Francisco. Cultural and educational activities abound. Please contact: Latimer Booth, MD, Chief, Department of Surgery, The Permanente Medical Group, 260 International Circle, San Jose, CA 95119 or telephone collect (408) 972-6010.

ASSOCIATE IN PEDIATRICS: Kern Medical Center, Bakersfield, California, a Southern California teaching hospital affiliated with UCLA School of Medicine, seeks an Associate in its Department of Pediatrics. Prerequisites include eligibility or certification by the American Board of Pediatrics, strong interest in teaching and qualifications for faculty appointment in the UCLA Department of Pediatrics. Compensation and benefits are competitive. Please reply with curriculum vitae to Jess Diamond, MD, Chairman, Kern Medical Center Department of Pediatrics, 1830 Flower St., Bakersfield, CA 93305, or telephone (collect) at (805) 326-2263.

OREGON COAST—Dynamic four-physician group seeks Board certified Internist on January 1, 1985. New clinic adjacent to hospital with sophisticated ICU. Beautiful coastal community. Phone (503) 738-9551 or (503) 738-7405. Ask for Dr Wolfe.

SAN FRANCISCO BAY AREA—60 MD multispecialty private group practice established 25 years ago, seeking a well-qualified Obstetrician Gynecologist to join our busy 5 physician department in their general OB/GYN work. Excellent location in the Santa Clara Valley, 45 minutes from San Francisco, 10 minutes from Stanford University. Send CV to: Recruitment Committee, PO Box 3496, Sunnyvale, CA 94088-3496.

STUDENT HEALTH SERVICE, University of Nevada-Reno: General medicine in outpatient clinic serving 7,000 students. Excellent fringe benefits including TIAA/CREF retirement plan. Malpractice insurance provided. 12-month annually renewable contract. 40 hour week. Eligibility for Nevada licensure required. Salary range $46,000-$50,000. Application deadline April 1, 1985. Starting date June 3, 1985. Send résumé to: Joseph S. Beres, MD, Director, Student Health Service, University of Nevada-Reno, Reno, NV 89557; Phone (702) 784-6598.

SAN FRANCISCO BAY AREA: Brand new primary care clinic fifteen minutes from downtown San Francisco seeks BE/BC primary care physician. Physicians interested in practice building, regular hours, guaranteed base plus profit sharing and stock options are invited to respond. Please send CV to Richard Miller, Director of Physician Services, CHEC Medical Centers, 2200 Sixth Ave., Suite 1200-BB, Seattle, WA 98121, or call collect (206) 728-6888.

GENERAL INTERNIST, BOARD CERTIFIED/ELIGIBLE: Multi-specialty group, university town central Washington, has space and services available on a lease or compensation basis with future partnership if desired. Contact A. J. Grose, MD, Medical Building Associates, PO Box 369, Ellensburg, WA 98926.

FP/GP to share practice and well-equipped office. (714) 848-4110. Edward Weir, MD, 8041 Newman Ave., Huntington Beach, CA 92647.

KETCHUM, SUN VALLEY, IDAHO: Internist, Surgeon, OB Gyn, Pediatrician, Orthopedist in multi-specialty, expanding, well-equipped clinic. Income moderate; quality of life highest. Dr Bryan Stone, PO Box 2198, Ketchum, ID 83340; (208) 726-9361.

NON-INVASIVE CARDIOLOGIST to join another cardiologist as part of ten-member Internal Medicine section in rapidly expanding HMO. No catheterization. Expertise in CCU, Swan-Ganz, pacemaker, echocardiography, treadmills necessary. Reply with CV to Paul Johnson, MD, Chief, Department of Internal Medicine, The Permanente Medical Group, Inc., 401 Bicentennial Way, Santa Rosa, CA 95401.

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A WORD TO THE WHYS

WHY AMA? While the AMA endorses competition in health care delivery that eliminates excess cost without compromising quality, the AMA actively opposes any legislative initiatives that would reduce quality of medical services. AMA leadership in making high quality, cost effective health care available to the American public: it's one more good reason why you should be a part of the AMA.

WHY AMA? Thanks to the Patient Medication Instruction program newly launched by the AMA, you can provide your patients with important supplementary drug information. Each patient information sheet (PMI) conveys information most relevant to the patient in easy-to-understand language. Helping your patients toward a better understanding of the drugs you prescribe: it's one more good reason why you should be a part of the AMA.

To Join, Contact your county or state medical society or write: Division of Membership, AMA, 535 North Dearborn Street, Chicago, Illinois 60610 or call collect, (312) 751-6196.

CONTINUING MEDICAL EDUCATION

(Continued from Page 285)

April 11-12—**Sommer Memorial Lectures.** Portland. Thursday-Friday. OHSU Library Auditorium. Contact: OHSU-CME.

May 10—**Hypertension.** Portland. Friday. OHSU Library Auditorium. Contact: OHSU-CME.

May 17—**Infectious Diseases in Clinical Practice.** Portland. Friday. OHSU Library Auditorium. Contact: OHSU-CME.

May 31-June 1—**Internal Medicine Update.** Portland. Friday-Saturday. Marriott Hotel. Contact: OHSU-CME.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah State Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. They also must meet the definition of Utah Approved CME Credit for the purpose of medical license reregistration in Utah. Accredited institutions wishing to list AMA Category 1/Utah Approved CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, Utah 84102; or phone (801) 355-5290. For information on CME accreditation or on the CME requirements of the Utah Physicians' Licensing Board, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution or the CME office for current details.

SPONSORS OF COURSES—ABBREVIATIONS

AF: Arthritis Foundation, 1174 East 2700 South, Salt Lake City 84117. (801) 466-9389.

CH: Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price, UT 84501. (801) 637-4800.

CWH: Cottonwood Hospital, 5770 South 300 East, Salt Lake City 84101. (801) 262-3461.

FHP: Family Health Program/Utah, 323 South Sixth East, Salt Lake City 84102. (801) 335-1234. Contact: Kay Schultz for course information.

HAFB: Hill Air Force Hospital, Hill Air Force Base 84406. (801) 777-1262.

HCH: Holy Cross Hospital, 1045 East First South, Salt Lake City 84102. (801) 350-4744.

LDSH: Latter-Day Saints Hospital, 325 8th Avenue, Salt Lake City 84143. (801) 350-1100.

MDH: McKay-Dee Hospital Center, 3939 Harrison Blvd., Ogden 84409. (801) 399-4141.

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PHYSICIANS WANTED

FAMILY PRACTICE/ORTHOPEDIC SURGEON—Board Certified or eligible to join multispecialty group in North San Diego county. Send CV to T. Haas, MD, 145 Thunder Dr., Vista, CA 92083 or call (619) 941-8840.

HEMATOLOGIST/ONCOLOGIST to join ten-member Internal Medicine section in rapidly expanding HMO. Reply with CV to Paul Johnson, MD, Chief, Department of Internal Medicine, The Permanente Medical Group, Inc., 401 Bicentennial Way, Santa Rosa, CA 95401.

GENERAL SURGEONS needed for long-term practice opportunity in Western Washington community within two hours of Seattle-Tacoma. Training and experience in Vascular or Pediatric Surgery desirable. Practice support package possible. Send CV and reference to Nancy Friedrich, The Friedrich Group, 9284 Ferncliff N.E., Bainbridge Island, WA 98110.

SAN FRANCISCO BAY AREA PUBLIC GRADUATE TRAINING HOSPITAL RECRUITING THREE INTERNISTS to manage inpatient general medical services as active faculty in the Internal Medicine Residency Training Program. Inpatient medicine will constitute the major portion of the job, but significant participation in the outpatient clinics is anticipated. Minimal qualifications include Board Certification in Internal Medicine, additional training in general medicine beyond residency and demonstrated excellence in teaching bedside medicine. Other factors of importance are academic standing, and preferably Board Eligibility/Certification in Endocrinology or Rheumatology. The positions are full-time with one month vacation and a requirement that 80% of the time will be spent in practicing/teaching general medicine. The positions would be salaried or on a personal services contract providing full professional liability coverage. Interested individuals please submit curriculum vitae to Box 6457, Western Journal of Medicine, 44 Gough St., San Francisco, CA 94103. Affirmative Action employer.

WANTED—MD OR PHYSICIANS ASSISTANT to Volunteer services; Denali National Park; June-September; Operate Community Clinic two days with salary; provide medical coverage three days per week at Denali without salary; room/board provided. Reply résumé: Superintendent, Box 9, McKinley Park, AK 99755; (907) 683-2294. Reply by February 28, 1985.

WASHINGTON COASTAL COMMUNITY serving a population of 65,000 is actively recruiting the following specialists: ENT, Emergency Physician and Emergency Director. A variety of practice support options are available, i.e. office space, relocation assistance, etc. Enjoy the support of major West Coast Catholic Hospital System. Community has close proximity to major recreational areas and easy access to Seattle and Portland. For information send CV and references to: Nancy Friedrich, The Friedrich Group, 9284 Ferncliff N.E., Bainbridge Island, WA 98110.

PHYSICIANS WANTED

DIRECTOR OF FAMILY PRACTICE: 233-bed teaching hospital with residencies in Family Practice, General Surgery, Internal Medicine, and OBS/GYN is seeking a Director of Family Practice. Position available April 1985. Responsible for administration and supervision of patient care and family practice training program. Candidates should be Board-certified in Family Practice and have significant experience in administrative and teaching responsibilities. Experience in a training program preferred. Salary negotiable depending on background and experience. For additional information, submit CV and references or contact J. D. Kortzeborn, MD, Medical Director, San Joaquin General Hospital, PO Box 1020, Stockton, CA 95201; (209) 982-1800, Ext. 3052. Affirmative action/equal opportunity employer.

GERIATRICIAN/INTERNIST to join full-time faculty of 65 in 500-bed acute care teaching hospital located in beautiful Santa Clara Valley, affiliated with Stanford University School of Medicine. Responsibilities include development and participation in comprehensive geriatric program. Salary and university appointment based on training and experience. IM Certification Required. We are an equal opportunity, affirmative action employer. Please address inquiries to Gary Steinke, MD, Director of Geriatric Program, 751 South Bascom Ave., San Jose, CA 95128.

NEPHROLOGIST—Board Certified or eligible, to join a 150 physician multispecialty prepaid medical group in Hawaii. Stimulating practice; Universty-affiliated teaching program; Excellent fringe benefits. Write: Hawaii Permanente Medical Group, Inc., 1697 Ala Moana Blvd., Honolulu, HA 96815. An Equal Opportunity Employer.

PHYSICIAN WANTED: Internist and FP Physician for small group practice in northern Idaho. Excellent outdoor recreational area. Write to Western Journal of Medicine, 44 Gough St., San Francisco, CA 94103.

MEDICAL EQUIPMENT

WE WISH TO PURCHASE used xerography equipment for mammography examinations. Please call collect at (707) 468-9335.

WHOLESALE ORTHOPEDIC SUPPLIES—For your quality orthopedic supplies at Wholesale Prices, write H & H Wholesale Orthopedic Supply for a free catalog and price list. Star Route-Box 446, Moses Lake, WA 98837

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LOCUM TENENS

LOCUM TENENS SERVICE
WESTERN PHYSICIANS REGISTRY

. . . offers coverage for vacation or continuing education. To arrange coverage for your practice or to participate as temporary physician, contact: **Carol Sweig, Director, 1124 Ballena, Alameda, CA 94501; (415) 521-4110.**

EVALUATION MEDICINE: Established and fast growing practice in San Francisco seeks specialist in Medical Toxicology. This is an excellent opportunity for the practitioner who wishes to supplement his/her income or for the semi-retired practitioner who desires only part time employment. This unique practice provides all management and support functions while allowing each physician complete flexibility in the scheduling of appointments. Please call or write Greg Blanchard, Medical Evaluation Specialists, 2233 Post St., Suite 304, San Francisco, CA 94115; (415) 563-4000.

SITUATIONS WANTED

GENERAL RADIOLOGIST seeks part-time position in rural or non-metropolitan area of California. Experienced in general diagnostic studies and CT. Prefer association with multi-specialty group. Reply to Box 6456, Western Journal of Medicine, 44 Gough St., San Francisco, CA 94103.

INTERNIST AVAILABLE: Board eligible internist educated Case Western Reserve seeks solo or group practice in Northern California. Available March 1985. Will also consider ER. Steven Wolinsky, MD, (201) 654-3649.

PRACTICES AVAILABLE

CALIFORNIA: Pathology, Radiology, Ophthalmology, OBG, Family, Internal, Surgery, Pediatric, Orthopedic, others. Contact: Mary Bradshaw, Practice broker/Recruiter, 21 Altamount Dr., Orinda, CA 94563; (415) 376-0762.

FAMILY PRACTICE NEAR BEAUTIFUL SAN DIEGO—Potential great! Ideal for young doctor wishing to develop practice and enjoy country living in San Diego County, California. Terms negotiable. Ward Peterson, MD, PO Box 547, Alpine, CA 92001; (619) 445-3242.

WELL ESTABLISHED FAMILY PRACTICE located in the San Joaquin Valley near Modesto. Office is well equipped and has an area of 1,800 square feet. Terms negotiable. Reply Box 6458, Western Journal of Medicine, 44 Gough St., San Francisco, CA 94103.

WELL ESTABLISHED FAMILY PRACTICE AND CLINIC FOR SALE: 1,600 Square feet, well-equipped with laboratory, x-ray and surgery. Will negotiate terms. Contact: J. Erickson, MD, Box 44488, Tacoma, WA 98444.

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PHYSICIANS
We are announcing opportunities for you to serve your country as an Air Force Reserve physician/officer. You can make new professional associations, obtain CME credit and help support the Air Force mission. For those who qualify, retirement credit can be obtained as well as low cost life insurance. One weekend a month plus two weeks a year or less can bring you pride and satisfaction in serving your country.
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A GREAT WAY TO SERVE

CONTINUING MEDICAL EDUCATION

(Continued from Page 289)

OEH: Rocky Mountain Center for Occupational and Environmental Health, 50 North Medical Drive, Salt Lake City 84132. (801) 581-8719.

OSS: Ogden Surgical Society, PO Box 9311, Ogden 84409.

PCMC: Primary Children's Medical Center, 320 12th Ave., Salt Lake City 84103. (801) 363-1221.

SHCC: Shriners Hospital for Crippled Children, Intermountain Unit, Fairfax Ave. at Virginia St., Salt Lake City 84103. (801) 532-5307.

SLSC: Salt Lake Surgical Center, 617 East 3900 South, Salt Lake City 84117. (801) 261-3141.

UAFP: Utah Academy of Family Physicians, 1146 Westminster Ave., Salt Lake City 84105. (801) 466-9478.

UUMC: University of Utah Medical Center, 50 North Medical Drive, Salt Lake City 84132. (801) 581-2258.

USMA: Utah State Medical Association, 540 East Fifth South, Salt Lake City 84102. (801) 355-7477.

UVH: Utah Valley Hospital, 1034 North Fifth West, Provo 84601. (801) 373-7850.

VAMC: Veterans Administration Medical Center, 500 Foothill Drive, Salt Lake City 84148. (801) 582-1565.

MEDICAL GRAND ROUNDS

Each Wednesday—8:00-9:00 a.m. Alternating between University of Utah Medical Center and VA Medical Center, Salt Lake City. Contact: William D. Odell, MD, PhD, Professor and Chairman, Dept. of Internal Medicine, Univ. of Utah, (801) 581-7606.

* * *

February 17-20—**26th Annual Ob/Gyn Update** (Sponsor: University of Utah). Sunday-Wednesday. Park City Holiday Inn/Yarrow. Fee to be announced. 14 hrs. Contact: Maria Vescio, (801) 581-7647.

February 20-23—**Reproductive Endocrinology and Infertility** (Sponsor: University of Utah). Wednesday-Saturday. Park City Holiday Inn/Yarrow. Fee to be announced. 14 hrs. Contact: Maria Vescio, (801) 581-7647.

February 22-26—**30th Annual Postgrad Course in Anesthesiology** (Sponsor: University of Utah). Friday-Tuesday. Salt Lake City. Fee to be announced. 16 hrs. Contact: Vicky Larsen, (801) 581-6115.

February 25-March 1—**Advances in Internal Medicine** (Sponsor: University of Utah). Monday-Friday. Snowbird. Fee to be announced. 25 hrs. Contact: Malcolm Berenson, MD, (801) 581-3581.

March 4-8—**Medical and Surgical Advances in Gastroenterology** (Sponsor: University of Utah). Monday-Friday. Snowbird. Fee to be announced. 25 hrs. Contact: Malcolm Berenson, MD, (801) 581-3581.

March 6-8—**Common Problems in Pediatrics VII** (Sponsor: University of Utah). Wednesday-Friday. Little America Hotel, Salt Lake City. Fee to be an-

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nounced. 12 hrs. Contact: Wendy Ellis, (801) 363-1887 or Robert Bolte, MD, (801) 363-1221.

March 12-22—**Transport Workshop: Neonatal-Maternal-Administration** (Sponsor: University of Utah). Tuesday-Friday. Salt Lake City. Fee to be announced. 69½ hrs. Contact: Anne Shanahan, (801) 581-2730.

March 18-22—**5th Annual Nutrition in Contemporary Medicine Symposium** (Sponsor: University of Utah). Monday-Friday. Park City. Fee to be announced. 29 hrs. Contact: M. Rita Thomas, MD, (801) 581-3581.

March 21-23—**Practical Neurology for Clinicians** (Sponsor: University of Utah). Thursday-Saturday. Sheraton Hotel, Salt Lake City. Fee to be announced. 18 hrs. Contact: Richard Baringer, MD, (801) 581-8664.

WASHINGTON

This listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121; or phone (206) 623-4801.

Brochures and Registration Forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

February 15—**Acute Abdominal Trauma.** Seattle. Friday. Riverton Hospital. Contact: U/W.

February 16—**Interventional Radiology of the Abdomen.** Seattle. Saturday. U/W South Campus Center. Contact: U/W.

February 16-23—(IDAHO) **Internal Medicine.** Sun Valley. Saturday-Saturday. Elkhorn Resort. Contact: U/W.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

CME PIERCE COUNTY—Contact: Mrs Maxine Bailey, Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 223-6898.

February 19—**Total and Home Parenteral Nutrition.** Seattle. Tuesday. Ballard Hospital. Contact: U/W.

February 20-22—(MONTANA) **Internal Medicine Review.** Great Falls, Billings, Missoula. Wednesday-Friday. Contact: U/W.

February 22—**Olympic Experience With Lung Functions.** Seattle. Friday. Riverton Hospital. Contact: U/W.

February 22-23—**Hemodynamic Monitoring Workshop.** Seattle. Friday-Saturday. Contact: VMMC.

February 23-March 2—(IDAHO) **Office Orthopaedics.** Sun Valley. Saturday- Saturday. Elkhorn Resort. Contact: U/W.

February 26—**Management of Pain.** Auburn. Tuesday. Auburn General Hospital. Contact: U/W.

March 1—**Thrombolytic Therapy of MI's.** Seattle. Friday. Riverton Hospital. Contact: U/W.

March 2-9—(HAWAII) **Medicine in China.** Kauai. Saturday-Saturday. Kauai Sheraton. Contact: U/W.

March 2-9—(IDAHO) **Electromyography.** Sun Valley. Saturday-Saturday. Elkhorn Resort. Contact: U/W.

March 8—**Thyroid Rx: What, Where, When?** Seattle. Friday. Riverton Hospital. Contact: U/W.

March 9-16—(HAWAII) **Imaging Solutions for the 80s.** Kona. Saturday-Saturday. Royal Waikoloa. Contact: U/W.

March 15—**Soft Tissue Surgery.** Seattle. Friday. Contact: VMMC.

March 15—**Small Computers in Medical Practice.** Seattle. Friday. Riverton Hospital. Contact: U/W.

March 16-23—(HAWAII) **Drug Therapy.** Maui. Saturday-Saturday. Royal Lahaina. Contact: U/W.

March 19—**Epilepsy.** Seattle. Tuesday. Ballard Hospital. Contact: U/W.

March 21-22—**Advances in Internal Medicine.** Seattle. Thursday-Friday. U/W HUB. Contact: U/W.

March 22—**Medicine in Mainland China.** Seattle. Friday. Riverton Hospital. Contact: U/W.

March 23—**Magnetic Resonance Imaging.** Seattle. Saturday. U/W South Campus Center. Contact: U/W.

March 23-30—(HAWAII) **Vascular Surgery.** Maui. Saturday-Saturday. Royal Lahaina. Contact: U/W.

March 26—**Alzheimer's Disease.** Auburn. Tuesday. Auburn General Hospital. Contact: U/W.

March 29—**Convulsing and Floppy Kids.** Seattle. Friday. Riverton Hospital. Contact: U/W.

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March 30-April 6—(HAWAII) **Neurology Update.** Maui. Saturday-Saturday. Royal Lahaina. Contact: U/W.

April 5—**Riverton Hospital Lectures.** Seattle. Friday. Riverton Hospital. Contact: U/W.

April 11-12—**DRG.** Seattle. Thursday-Friday. Westin. Contact: U/W.

April 12—**Riverton Hospital Lectures.** Seattle. Friday. Riverton Hospital. Contact: U/W.

April 13—**Handicapped Infant.** Seattle. Saturday. U/W Health Sciences. Contact: U/W.

April 13—**Mason Clinic Day.** Seattle. Saturday. Contact: VMMC.

April 16—**Alzheimer's Disease.** Seattle. Tuesday. Ballard Hospital. Contact: U/W.

April 17-19—(MONTANA) **Internal Medicine Review.** Great Falls, Billings, Missoula. Wednesday-Friday. Contact: U/W.

April 18-20—**Death Investigation.** Seattle. Thursday-Saturday. Westin. Contact: U/W.

April 19—**Riverton Hospital Lectures.** Seattle. Friday. Riverton Hospital. Contact: U/W.

April 22-May 3—**Rehab Medicine Review.** Seattle. 12 days. Seattle Sheraton. Contact: U/W.

April 23—**Sexually Transmitted Diseases.** Auburn. Tuesday. Auburn General Hospital. Contact: U/W.

April 26—**Riverton Hospital Lectures.** Seattle. Friday. Riverton Hospital. Contact: U/W.

April 26-27—**Sexual Assault.** Seattle. Friday-Saturday. Westin Hotel. Contact: U/W.

May 3—**Riverton Hospital Lectures.** Seattle. Friday. Riverton Hospital. Contact: U/W.

May 3-4—**Pharmacology Update.** Seattle. Friday-Saturday. Contact: VMMC.

May 9-10—**Issues in General Pediatrics.** Seattle. Thursday-Friday. Children's Orthopedic Hospital. Contact: U/W.

May 10—**Riverton Hospital Lectures.** Seattle. Friday. Riverton Hospital. Contact: U/W.

May 17—**Riverton Hospital Lectures.** Seattle. Friday. Riverton Hospital. Contact: U/W.

May 18—**Microcomputers in Rehab Medicine.** Seattle. Saturday. Contact: U/W.

May 21—**Using Pulmonary Function Tests.** Seattle. Tuesday. Ballard Hospital. Contact: U/W.

May 22-24—(MONTANA) **Internal Medicine Review.** Great Falls, Billings, Missoula. Wednesday-Friday. Contact: U/W.

May 28—**Travel and Illness.** Auburn. Tuesday. Auburn General Hospital. Contact: U/W.

May 30-31—**Controversies in Cardiovascular Issues.** Seattle. Thursday-Friday. Contact: U/W.

May 30-31—**Mental Health Policy Forum.** Seattle. Thursday-Friday. Westin. Contact: U/W.

May 31—**Riverton Hospital Lectures.** Seattle. Friday. Riverton Hospital. Contact: U/W.

June 6-7—**Behavioral Medicine.** Seattle. Thursday-Friday. Westin. Contact: U/W.

June 6-8—**Medical Emergencies.** Seattle. Thursday-Saturday. Contact: VMMC.

June 7—**Riverton Hospital Lectures.** Seattle. Friday. Riverton Hospital. Contact: U/W.

June 13-14—**Ischemic Heart Disease.** Seattle. Thursday-Friday. Westin. Contact: U/W.

June 13-14—**Advances in Internal Medicine.** Seattle. Thursday-Friday. U/W HUB. Contact: U/W.

June 14—**Riverton Hospital Lectures.** Seattle. Friday. Riverton Hospital. Contact: U/W.

June 15—**Contemporary Thoracic Imaging.** Seattle. Saturday. U/W South Campus Center. Contact: U/W.

June 18—**Small Computers in Medicine.** Seattle. Tuesday. Ballard Hospital. Contact: U/W.

June 19-20—**Financial Planning for Physicians.** Victoria, BC. Wednesday-Friday. Empress Hotel. Contact: U/W.

June 21—**Riverton Hospital Lectures.** Seattle. Friday. Riverton Hospital. Contact: U/W.

June 21-22—**Nutrition of Hospitalized Patient.** Vancouver, BC. Saturday-Sunday. Contact: U/W.

June 25—**What's New in Antibiotics.** Auburn. Tuesday. Auburn General Hospital. Contact: U/W.

June 28—**Riverton Hospital Lectures.** Seattle. Friday. Riverton Hospital. Contact: U/W.

July 8-10—**Scientific Aspects of Dance/Exercising Women.** Seattle. Monday-Wednesday. Westin. Contact: U/W.

WYOMING

June 23-26—**Wyoming Medical Society—Annual Meeting.** Jackson Lake Lodge, Moran. Sunday-Wednesday. Contact: WMS, PO Drawer 4009, Cheyenne 82003-4009. ◆

WESTERN STATE MEDICAL ASSOCIATIONS' MEETINGS

Alaska State Medical Association—4107 Laurel St., Anchorage 99504. (907) 562-2662. Annual Meeting: June 8-11, 1985, Haines.

Arizona Medical Association, Inc.—810 W. Bethany Home Rd., Phoenix 85013. (602) 246-8901. Annual Meeting: April 26-27, 1985, The Cottonwoods, Scottsdale.

California Medical Association—44 Gough St., San Francisco 94103. (415) 863-5522. Annual Meeting: March 8-13, 1985, Town and County, San Diego.

Colorado Medical Society—6825 E. Tennessee, Bldg. 2, Suite 500, Denver 80224. (303) 321-8590. Annual Meeting: September 11-14, 1985, Broadmoor, Colorado Springs.

Hawaii Medical Association—320 Ward Ave., Suite 200, Honolulu 96814. (808) 536-7702. Annual Meeting: 1985—date and place to be announced.

Idaho Medical Association—407 W. Bannock St., PO Box 2668, Boise 83701. (208) 344-7888. Annual Meeting: July 24-27, 1985, Sun Valley.

Montana Medical Association—2012 11th Ave., Suite 12, Helena 59601. (406) 443-4000. Annual Meeting: October 3-5, 1985, Outlaw Inn, Kalispell.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: May 9-12, 1985, Hyatt, Lake Tahoe.

New Mexico Medical Society—303 San Mateo NE, Suite 204, Albuquerque 87108. (505) 266-7868. Annual Meeting: May 1-3, 1985, Marriott, Albuquerque.

Oregon Medical Association—5210 S.W. Corbett Ave., Portland 97201. (503) 226-1555. Annual Meeting: (House of Delegates only): April 26-28, 1985, Ashland Hills Inn, Ashland.

Utah State Medical Association—540 East Fifth South, Salt Lake City 84102. (801) 355-7477. Annual Meeting: September 26-27, 1985. Hotel Utah, Salt Lake City.

Washington State Medical Association—900 United Airlines Bldg., 2033 6th Ave., Seattle 98121. (206) 623-4801. Annual Meeting: September 19-22, 1985, Jantzen Beach.

Wyoming Medical Society—P.O. Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. Annual Meeting: June 23-26, 1985, Jackson Lake Lodge, Moran.

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Warnings: Use with great care in patients with history of urinary retention or angle-closure glaucoma. Severe constipation may occur in patients taking tricyclic antidepressants and anticholinergic-type drugs. Closely supervise cardiovascular patients (Arrhythmias, sinus tachycardia and prolongation of conduction time reported with use of tricyclic antidepressants, especially high doses. Myocardial infarction and stroke reported with use of this class of drugs.) Caution patients about possible combined effects with alcohol and other CNS depressants and against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving).

Usage in Pregnancy: **Use of minor tranquilizers during the first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Since physical and psychological dependence to chlordiazepoxide have been reported rarely, use caution in administering Limbitrol to addiction-prone individuals or those who might increase dosage; withdrawal symptoms following discontinuation of either component alone have been reported (nausea, headache and malaise for amitriptyline; symptoms [including convulsions] similar to those of barbiturate withdrawal for chlordiazepoxide).

Precautions: Use with caution in patients with a history of seizures, in hyperthyroid patients or those on thyroid medication, and in patients with impaired renal or hepatic function. Because of the possibility of suicide in depressed patients, do not permit easy access to large quantities in these patients. Periodic liver function tests and blood counts are recommended during prolonged treatment. Amitriptyline component may block action of guanethidine or similar antihypertensives. Concomitant use with other psychotropic drugs has not been evaluated, sedative effects may be additive. Discontinue several days before surgery. Limit concomitant administration of ECT to essential treatment. See Warnings for precautions about pregnancy. Limbitrol should not be taken during the nursing period. Not recommended in children under 12. In the elderly and debilitated, limit to smallest effective dosage to preclude ataxia, oversedation, confusion or anticholinergic effects.

Adverse Reactions: Most frequently reported are those associated with either component alone: drowsiness, dry mouth, constipation, blurred vision, dizziness and bloating. Less frequently occurring reactions include vivid dreams, impotence, tremor, confusion and nasal congestion. Many depressive symptoms including anorexia, fatigue, weakness, restlessness and lethargy have been reported as side effects of both Limbitrol and amitriptyline. Granulocytopenia, jaundice and hepatic dysfunction have been observed rarely.

The following list includes adverse reactions not reported with Limbitrol but requiring consideration because they have been reported with one or both components or closely related drugs:

Cardiovascular: Hypotension, hypertension, tachycardia, palpitations, myocardial infarction, arrhythmias, heart block, stroke.

Psychiatric: Euphoria, apprehension, poor concentration, delusions, hallucinations, hypomania and increased or decreased libido.

Neurologic: Incoordination, ataxia, numbness, tingling and paresthesias of the extremities, extrapyramidal symptoms, syncope, changes in EEG patterns.

Anticholinergic: Disturbance of accommodation, paralytic ileus, urinary retention, dilatation of urinary tract.

Allergic: Skin rash, urticaria, photosensitization, edema of face and tongue, pruritus.

Hematologic: Bone marrow depression including agranulocytosis, eosinophilia, purpura, thrombocytopenia.

Gastrointestinal: Nausea, epigastric distress, vomiting, anorexia, stomatitis, peculiar taste, diarrhea, black tongue.

Endocrine: Testicular swelling and gynecomastia in the male, breast enlargement, galactorrhea and minor menstrual irregularities in the female, elevation and lowering of blood sugar levels, and syndrome of inappropriate ADH (antidiuretic hormone) secretion.

Other: Headache, weight gain or loss, increased perspiration, urinary frequency, mydriasis, jaundice, alopecia, parotid swelling.

Overdosage: Immediately hospitalize patient suspected of having taken an overdose. Treatment is symptomatic and supportive. I.V. administration of 1 to 3 mg physostigmine salicylate has been reported to reverse the symptoms of amitriptyline poisoning. See complete product information for manifestation and treatment.

Dosage: Individualize according to symptom severity and patient response. Reduce to smallest effective dosage when satisfactory response is obtained. Larger portion of daily dose may be taken at bedtime. Single *h.s.* dose may suffice for some patients. Lower dosages are recommended for the elderly.

Limbitrol DS (double strength) Tablets, initial dosage of three or four tablets daily in divided doses, increased to six tablets or decreased to two tablets daily as required. Limbitrol Tablets, initial dosage of three or four tablets daily in divided doses, for patients who do not tolerate higher doses.

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Official Journal of the California Medical Association, the Idaho Medical Association, the Nevada State Medical Association, the New Mexico Medical Society, the Utah State Medical Association, the Washington State Medical Association and the Wyoming Medical Society.

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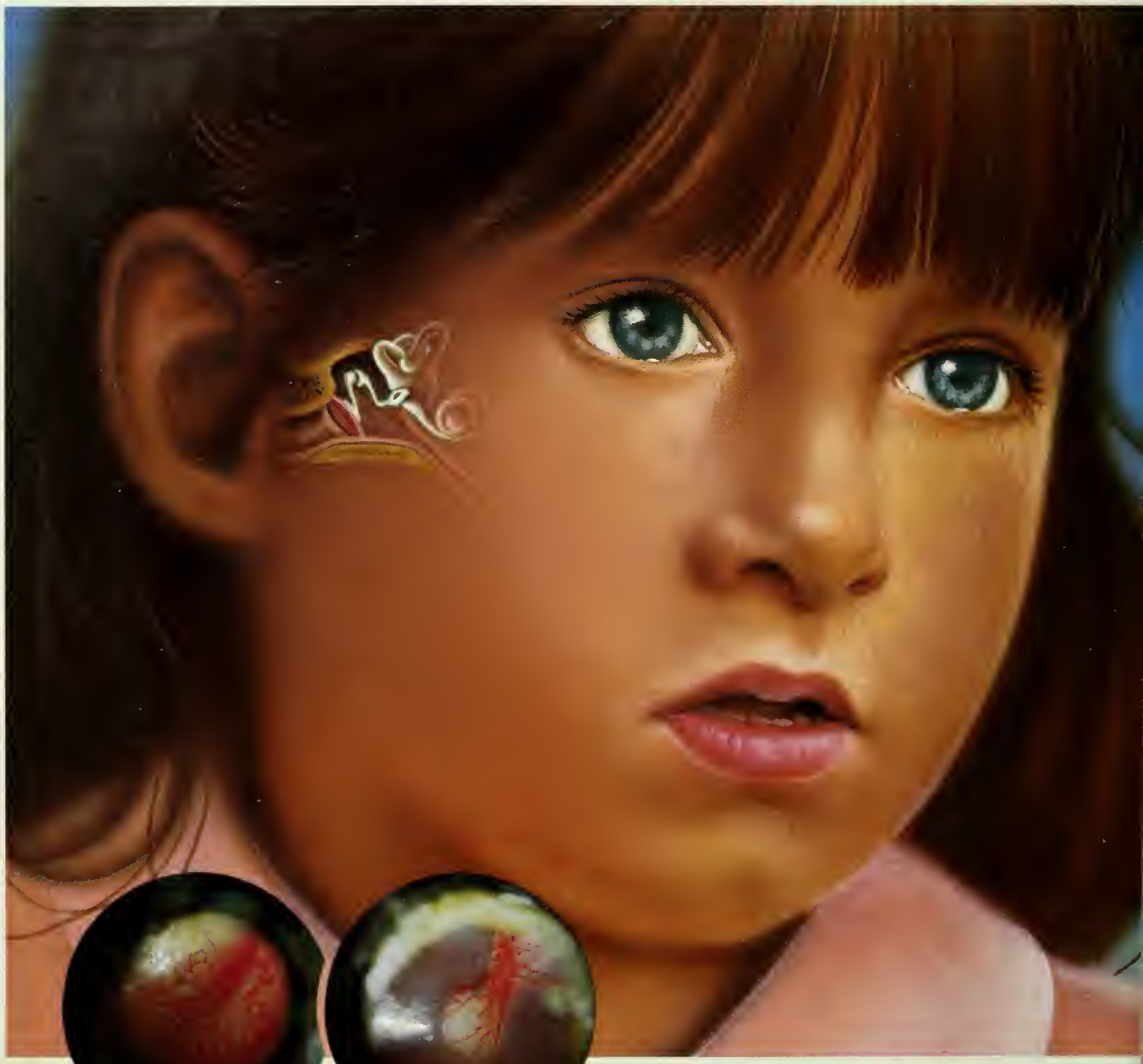

before Otoscopic view of tympanic membrane in a patient who did not respond to ampicillin

after Same patient after ten days of Bactrim (trimethoprim and sulfamethoxazole/Roche) therapy

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ctive against 86% of *H. influenzae in vitro*—even amoxicillin- nd ampicillin-resistant strains

verall, 86% of *Haemophilus influenzae* strains taken from sputum cultures prove sceptible *in vitro* to Bactrim.[4] In one study, 100% of 191 ampicillin-resistant *. influenzae* isolates were susceptible to Bactrim.[5] However, *in vitro* data do not cessarily correlate with clinical results.

ctive against 91% of *S. pneumoniae in vitro*

sputum cultures of *Streptococcus pneumoniae*, the most frequent pathogen in acute itis media, 91% of isolates show susceptibility *in vitro* to Bactrim.[4]

xcellent clinical activity—and economical

comparative clinical trials in children with acute otitis media, Bactrim *b.i.d.* was surpassed by ampicillin, amoxicillin or cefaclor.[6]
nd the average cost of Bactrim is lower than that of cefaclor and comparable to that ampicillin and amoxicillin.[7]
actrim is indicated in acute otitis media due to susceptible organisms when it offers advantage over other antimicrobials. Bactrim is contraindicated in pregnancy, ctation, infants under two months of age and documented megaloblastic anemia ue to folate deficiency. To date, there are limited data on the safety of repeated use Bactrim in children under two years of age.

Cherry-flavored suspension

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(trimethoprim and sulfamethoxazole/Roche)

B.I.D. for enhanced compliance.

Please see references and summary of product information on following page.

References: 1. Klimek JJ *et al*: *J Pediatr* 96:1087-1089, Jun 1980. 2. Schwartz RH *et al*: *Rev Infect Dis* 4:514-516, Mar-Apr 1982. 3. Cooper J, Inman JS, Dawson AF: *Practitioner* 217:804-809, Nov 1976. 4. Antibiotic Sensitivity Report, Winter 1983. BAC-DATA Medical Information Systems, Inc. 5. Data on file, Hoffmann-La Roche Inc., Nutley, NJ. 6. Wormser GP, Keusch GT, Heel RC: *Drugs* 24:459-518, Dec 1982. 7. *Med Lett Drugs Ther* 23:93-95, Oct 30, 1981.

BACTRIM™ (trimethoprim and sulfamethoxazole/Roche)

Before prescribing, please consult complete product information, a summary of which follows:

Indications and Usage: For the treatment of urinary tract infections due to susceptible strains of the following organisms: *Escherichia coli, Klebsiella-Enterobacter, Proteus mirabilis, Proteus vulgaris, Proteus morganii.* It is recommended that initial episodes of uncomplicated urinary tract infections be treated with a single effective antibacterial agent rather than the combination. *Note:* The increasing frequency of resistant organisms limits the usefulness of all antibacterials, especially in these urinary tract infections.

For acute otitis media in children due to susceptible strains of *Haemophilus influenzae* or *Streptococcus pneumoniae* when in physician's judgment it offers an advantage over other antimicrobials. To date, there are limited data on the safety of repeated use of Bactrim in children under two years of age. Bactrim is not indicated for prophylactic or prolonged administration in otitis media at any age.

For acute exacerbations of chronic bronchitis in adults due to susceptible strains of *Haemophilus influenzae* or *Streptococcus pneumoniae* when in physician's judgment it offers an advantage over a single antimicrobial agent.

For enteritis due to susceptible strains of *Shigella flexneri* and *Shigella sonnei* when antibacterial therapy is indicated.

Also for the treatment of documented *Pneumocystis carinii* pneumonitis.

Contraindications: Hypersensitivity to trimethoprim or sulfonamides; patients with documented megaloblastic anemia due to folate deficiency; pregnancy at term; nursing mothers because sulfonamides are excreted in human milk and may cause kernicterus; infants less than 2 months of age.

Warnings: BACTRIM SHOULD NOT BE USED TO TREAT STREPTOCOCCAL PHARYNGITIS. Clinical studies show that patients with group A β-hemolytic streptococcal tonsillopharyngitis have higher incidence of bacteriologic failure when treated with Bactrim than do those treated with penicillin. Deaths from hypersensitivity reactions, hepatocellular necrosis, agranulocytosis, aplastic anemia and other blood dyscrasias have been associated with sulfonamides. Experience with trimethoprim is much more limited but occasional interference with hematopoiesis has been reported as well as an increased incidence of thrombopenia with purpura in elderly patients on certain diuretics, primarily thiazides. Sore throat, fever, pallor, purpura or jaundice may be early signs of serious blood disorders. Frequent CBC's are recommended; therapy should be discontinued if a significantly reduced count of any formed blood element is noted.

Precautions: *General:* Use cautiously in patients with impaired renal or hepatic function, possible folate deficiency, severe allergy or bronchial asthma. In patients with glucose-6-phosphate dehydrogenase deficiency, hemolysis, frequently dose-related, may occur. During therapy, maintain adequate fluid intake and perform frequent urinalyses, with careful microscopic examination, and renal function tests, particularly where there is impaired renal function. Bactrim may prolong prothrombin time in those receiving warfarin; reassess coagulation time when administering Bactrim to these patients.

Pregnancy: Teratogenic Effects: Pregnancy Category C. Because trimethoprim and sulfamethoxazole may interfere with folic acid metabolism, use during pregnancy only if potential benefits justify the potential risk to the fetus.

Adverse Reactions: All major reactions to sulfonamides and trimethoprim are included, even if not reported with Bactrim. *Blood dyscrasias:* Agranulocytosis, aplastic anemia, megaloblastic anemia, thrombopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia and methemoglobinemia. *Allergic reactions:* Erythema multiforme, Stevens-Johnson syndrome, generalized skin eruptions, epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia and allergic myocarditis. *Gastrointestinal reactions:* Glossitis, stomatitis, nausea, emesis, abdominal pains, hepatitis, hepatocellular necrosis, diarrhea, pseudomembranous colitis and pancreatitis. *CNS reactions:* Headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo, insomnia, apathy, fatigue, muscle weakness and nervousness. *Miscellaneous reactions:* Drug fever, chills, toxic nephrosis with oliguria and anuria, periarteritis nodosa and L.E. phenomenon. Due to certain chemical similarities to some goitrogens, diuretics (acetazolamide, thiazides) and oral hypoglycemic agents, sulfonamides have caused rare instances of goiter production, diuresis and hypoglycemia in patients; cross-sensitivity with these agents may exist. In rats, long-term therapy with sulfonamides has produced thyroid malignancies.

Dosage: Not recommended for infants less than two months of age.

URINARY TRACT INFECTIONS AND SHIGELLOSIS IN ADULTS AND CHILDREN, AND ACUTE OTITIS MEDIA IN CHILDREN:

Adults: Usual adult dosage for urinary tract infections—1 DS tablet (double strength), 2 tablets (single strength) or 4 teasp. (20 ml) b.i.d. for 10-14 days. Use identical daily dosage for 5 days for shigellosis.

Children: Recommended dosage for children with urinary tract infections or acute otitis media—8 mg/kg trimethoprim and 40 mg/kg sulfamethoxazole per 24 hours, in two divided doses for 10 days. Use identical daily dosage for 5 days for shigellosis.

For patients with renal impairment: Use recommended dosage regimen when creatinine clearance is above 30 ml/min. If creatinine clearance is between 15 and 30 ml/min, use one-half the usual regimen. Bactrim is not recommended if creatinine clearance is below 15 ml/min.

ACUTE EXACERBATIONS OF CHRONIC BRONCHITIS IN ADULTS:

Usual adult dosage: 1 DS tablet (double strength), 2 tablets (single strength) or 4 teasp. (20 ml) b.i.d. for 14 days.

PNEUMOCYSTIS CARINII PNEUMONITIS:

Recommended dosage: 20 mg/kg trimethoprim and 100 mg/kg sulfamethoxazole per 24 hours in equal doses every 6 hours for 14 days. See complete product information for suggested children's dosage table.

Supplied: *Double Strength (DS) tablets,* each containing 160 mg trimethoprim and 800 mg sulfamethoxazole, bottles of 100, 250 and 500; Tel-E-Dose® packages of 100; Prescription Paks of 20. *Tablets,* each containing 80 mg trimethoprim and 400 mg sulfamethoxazole—bottles of 100 and 500; Tel-E-Dose® packages of 100; Prescription Paks of 40. *Pediatric Suspension,* containing 40 mg trimethoprim and 200 mg sulfamethoxazole per teaspoonful (5 ml); cherry flavored—bottles of 100 ml and 16 oz (1 pint). *Suspension,* containing 40 mg trimethoprim and 200 mg sulfamethoxazole per teaspoonful (5 ml); fruit-licorice flavored—bottles of 16 oz (1 pint).

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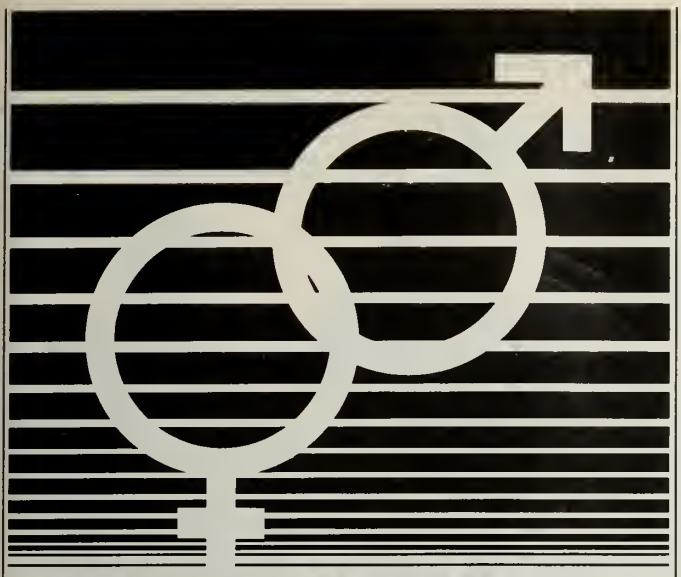

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The sublingual and chewable forms of the drug are indicated for acute prophylaxis of angina pectoris when taken a few minutes before situations likely to provoke anginal attacks. Because of a slower onset of effect, the oral forms of isosorbide dinitrate are not indicated for acute prophylaxis.

CONTRAINDICATIONS: SORBITRATE is contraindicated in patients who have shown purported hypersensitivity or idiosyncrasy to it or other nitrates or nitrites. Epinephrine and related compounds are ineffective in reversing the severe hypotensive events associated with overdose and are contraindicated in this situation.

WARNINGS: The benefits of SORBITRATE during the early days of an acute myocardial infarction have not been established. If one elects to use organic nitrates in early infarction, hemodynamic monitoring and frequent clinical assessment should be used because of the potential deleterious effects of hypotension.

PRECAUTIONS: General: Severe hypotensive response, particularly with upright posture, may occur with even small doses of SORBITRATE. The drug should therefore be used with caution in subjects who may have blood volume depletion from diuretic therapy or in subjects who have low systolic blood pressure (eg, below 90 mmHg). Paradoxical bradycardia and increased angina pectoris may accompany nitrate-induced hypotension. Nitrate therapy may aggravate the angina caused by hypertrophic cardiomyopathy.

Marked symptomatic, orthostatic hypotension has been reported when calcium channel blockers and organic nitrates were used in combination. Dose adjustment of either class of agents may be necessary.

Tolerance to this drug and cross-tolerance to other nitrates and nitrites may occur. Tolerance to the vascular and antianginal effects of isosorbide dinitrate or nitroglycerin has been demonstrated in clinical trials, experience through occupational exposure, and in isolated tissue experiments in the laboratory. The importance of tolerance to the appropriate use of isosorbide dinitrate in the management of patients with angina pectoris has not been determined. However, one clinical trial using treadmill exercise tolerance (as an end point) found an 8-hour duration of action of oral isosorbide dinitrate following the first dose (after a 2-week placebo washout) and only a 2-hour duration of effect of the same dose after 1 week of repetitive dosing at conventional dosing intervals. On the other hand, several trials have been able to differentiate isosorbide dinitrate from placebo after 4 weeks of therapy and, in open trials, an effect seems detectable for as long as several months.

Tolerance clearly occurs in industrial workers continuously exposed to nitroglycerin. Moreover, physical dependence also occurs since chest pain, acute myocardial infarction, and even sudden death have occurred during temporary withdrawal of nitroglycerin from the workers. In clinical trials in angina patients, there are reports of anginal attacks being more easily provoked and of rebound in the hemodynamic effects soon after nitrate withdrawal. The relative importance of these observations to the routine, clinical use of isosorbide dinitrate is not known. However, it seems prudent to gradually withdraw patients from isosorbide dinitrate when the therapy is being terminated, rather than stopping the drug abruptly.

Information for Patients: Headache may occur during initial therapy with SORBITRATE. Headache is usually relieved by the use of standard headache remedies or by lowering the dose and tends to disappear after the first week or two of use.

Drug Interactions: Alcohol may enhance any marked sensitivity to the hypotensive effect of nitrates.

Isosorbide dinitrate acts directly on vascular smooth muscle, therefore, any other agent that depends on vascular smooth muscle as the final common path can be expected to have decreased or increased effect depending on the agent.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No long-term studies in animals have been performed to evaluate the carcinogenic potential of this drug. A modified two-litter reproduction study in rats fed isosorbide dinitrate at 25 or 100 mg/kg/day did not reveal any effects on fertility or gestation or any remarkable gross pathology in any parent or offspring fed isosorbide dinitrate as compared with rats fed a basal-controlled diet.

Pregnancy Category C: Isosorbide dinitrate has been shown to cause a dose-related increase in embryotoxicity (increase in mummified pups) in rabbits at oral doses 35 and 150 times the maximum recommended human daily dose. There are no adequate and well-controlled studies in pregnant women. SORBITRATE should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when SORBITRATE is administered to a nursing woman.

Pediatric Use: The safety and effectiveness of SORBITRATE in children has not been established.

ADVERSE REACTIONS: Adverse reactions, particularly headache and hypotension, are dose-related. In clinical trials at various doses, the following have been observed.

Headache is the most common (reported incidence varies widely, apparently being dose-related, with an average occurrence of about 25%) adverse reaction and may be severe and persistent. Cutaneous vasodilation with flushing may occur. Transient episodes of dizziness and weakness, as well as other signs of cerebral ischemia associated with postural hypotension, may occasionally develop (the incidence of reported symptomatic hypotension ranges from 2% to 36%). An occasional individual will exhibit marked sensitivity to the hypotensive effects of nitrates and severe responses (nausea, vomiting, weakness, restlessness, pallor, perspiration, and collapse) may occur even with the usual therapeutic dose. Drug rash and/or exfoliative dermatitis may occasionally occur. Nausea and vomiting appear to be uncommon. Case reports of clinically significant methemoglobinemia are rare at conventional doses of organic nitrates. The formation of methemoglobin is dose-related and, in the case of genetic abnormalities of hemoglobin that favor methemoglobin formation, even conventional doses of organic nitrate could produce harmful concentrations of methemoglobin.

DOSAGE AND ADMINISTRATION: For the treatment of angina pectoris, the usual starting dose for sublingual SORBITRATE is 2.5 to 5 mg, for chewable tablets, 5 mg, for oral (swallowed) tablets, 5 to 20 mg, and for controlled-release forms, 40 mg.

SORBITRATE should be titrated upward until angina is relieved or side effects limit the dose. In ambulatory patients, the magnitude of the incremental dose increase should be guided by measurements of standing blood pressure.

The initial dosage of sublingual or chewable SORBITRATE for prophylactic therapy in angina pectoris patients is generally 5 or 10 mg every 2 to 3 hours. Adequate controlled clinical studies demonstrating the effectiveness of chronic maintenance therapy with these dosage forms have not been reported.

SORBITRATE in oral doses of 10 to 40 mg given every 6 hours or in oral controlled-release doses of 40 to 80 mg given every 8 to 12 hours is generally recommended. The extent to which development of tolerance should modify the dosage program has not been defined. *The oral controlled-release forms of isosorbide dinitrate should not be chewed.*

DOSAGE FORMS AVAILABLE: Sublingual Tablets (2.5, 5, 10 mg); Chewable Tablets (5, 10 mg); Oral Tablets (5, 10, 20, 30, 40 mg); Sustained Action Tablets (40 mg).

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CONTRAINDICATIONS: Bronchial asthma, sinus bradycardia and greater than first degree conduction block, cardiogenic shock, and overt cardiac failure (see WARNINGS).

WARNINGS: Cardiac Failure–Sympathetic stimulation may be a vital component supporting circulatory function in congestive heart failure, and its inhibition by beta-blockade may precipitate more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, they can be used with caution in patients with a history of failure who are well-compensated, usually with digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle. IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta-blockers can, in some cases, lead to cardiac failure; therefore, at first sign or symptom of heart failure, digitalize and/or give diuretics, and closely observe response, or discontinue nadolol (gradually if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal– Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred alter *abrupt* discontinuation of such therapy. When discontinuing chronic use of nadolol, particularly in patients with ischemic heart disease, gradually reduce dosage over a 1- to 2-week period and carefully monitor the patient. Reinstitute nadolol promptly (at least temporarily) and take other measures appropriate for management of unstable angina if angina markedly worsens or acute coronary insufficiency develops. Warn patients not to interrupt or discontinue therapy without physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue nadolol therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)– PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA-BLOCKERS. Administer nadolol with caution since it may block bronchodilation produced by endogenous or exogenous catecholamine stimulation of $beta_2$ receptors.

Major Surgery–Because beta blockade impairs the ability of the heart to respond to reflex stimuli and may increase risks of general anesthesia and surgical procedures, resulting in protracted hypotension or low cardiac output, it has generally been suggested that such therapy should be withdrawn several days prior to surgery. Recognition of the increased sensitivity to catecholamines of patients recently withdrawn from beta-blocker therapy, however, has made this recommendation controversial. If possible, withdraw beta-blockers well before surgery takes place. In emergency surgery, inform the anesthesiologist that the patient is on beta-blocker therapy. Use of beta-receptor agonists such as isoproterenol, dopamine, dobutamine, or levarterenol can reverse the effects of nadolol. Difficulty in restarting and maintaining the heart beat has also been reported with beta-adrenergic receptor blocking agents.

Diabetes and Hypoglycemia–Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia and blood pressure changes) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces release of insulin in response to hyperglycemia; therefore, it may be necessary to adjust dose of antidiabetic drugs.

Thyrotoxicosis–Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. To avoid abrupt withdrawal of beta-adrenergic blockade which might precipitate a thyroid storm, carefully manage patients suspected of developing thyrotoxicosis.

PRECAUTIONS: Impaired Hepatic or Renal Function–Use nadolol with caution in presence of either of these conditions (see DOSAGE AND ADMINISTRATION section of package insert).

Information for Patients–Warn patients, especially those with evidence of coronary artery insufficiency, against interruption or discontinuation of nadolol without physician's advice. Although cardiac failure rarely occurs in properly selected patients, advise patients being treated with beta-adrenergic blocking agents to consult physician at first sign or symptom of impending failure.

Drug Interactions–Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. When treating patients with nadolol plus a catecholamine-depleting agent, carefully observe for evidence of hypotension and/or excessive bradycardia which may produce vertigo, syncope, or postural hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility–In 1 to 2 years' oral toxicologic studies in mice, rats, and dogs, nadolol did not produce significant toxic effects. In 2-year oral carcinogenic studies in rats and mice, nadolol did not produce neoplastic, preneoplastic, or nonneoplastic pathologic lesions.

Pregnancy–In animal reproduction studies with nadolol, evidence of embryo-and fetotoxicity was found in rabbits (but not in rats or hamsters) at doses 5 to 10 times greater (on a mg/kg basis) than maximum indicated human dose; no teratogenic potential was seen in any of these species. There are no well-controlled studies in pregnant women; therefore, use nadolol in pregnant women only if potential benefit justifies potential risk to the fetus.

Nursing Mothers–It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when nadolol is administered to a nursing woman. Animal studies showed that nadolol is found in the milk of lactating rats.

Pediatric Use–Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects have been mild and transient and have rarely required nadolol withdrawal.

Cardiovascular–Bradycardia with heart rates of less than 60 beats per minute occurs commonly, and heart rates below 40 beats per minute and/or symptomatic bradycardia were seen in about 2 of 100 patients. Symptoms of peripheral vascular insufficiency, usually of the Raynaud type, have occurred in approximately 2 of 100 patients. Cardiac failure, hypotension, and rhythm/conduction disturbances have each occurred in about 1 of 100 patients. Single instances of first degree and third degree heart block have been reported; intensification of AV block is a known effect of beta-blockers (see also CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS). **Central Nervous System**–Dizziness or fatigue reported in approximately 2 of 100 patients; paresthesias, sedation, and change in behavior reported in approximately 6 of 1000 patients. **Respiratory**–Bronchospasm reported in approximately 1 of 1000 patients (see CONTRAINDICATIONS and WARNINGS). **Gastrointestinal**– Nausea, diarrhea, abdominal discomfort, constipation, vomiting, indigestion, anorexia, bloating, and flatulence each reported in 1 to 5 of 1000 patients. **Miscellaneous**–Each of the following reported in 1 to 5 of 1000 patients: rash; pruritus; headache; dry mouth, eyes, or skin; impotence or decreased libido; facial swelling; weight gain; slurred speech; cough; nasal stuffiness; sweating; tinnitus; blurred vision. Although relationship to drug usage is not clear, sleep disturbances have been reported. The oculomucocutaneous syndrome associated with practolol has not been reported with nadolol.

Potential Adverse Effects: Although other adverse effects reported with other beta-adrenergic blocking agents have not been reported with nadolol, they should be considered potential adverse effects of nadolol. **Central Nervous System**–reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place; short-term memory loss, emotional lability with slightly clouded sensorium; decreased performance on neuropsychometrics. **Gastrointestinal**–mesenteric arterial thrombosis; ischemic colitis. **Hematologic**–agranulocytosis; thrombocytopenic or nonthrombocytopenic purpura. **Allergic**–fever combined with aching and sore throat; laryngospasm; respiratory distress. **Miscellaneous**–reversible alopecia; Peyronie's disease; erythematous rash.

OVERDOSAGE: Nadolol can be removed from the general circulation by hemodialysis. In addition to gastric lavage, employ the following measures as appropriate. In determining duration of corrective therapy, take note of long duration of effect of nadolol.

Excessive Bradycardia–Administer atropine (0.25 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.

Cardiac Failure–Administer a digitalis glycoside and diuretic. It has been reported that glucagon may also be useful in this situation.

Hypotension–Administer vasopressors, e.g., epinephrine or levarterenol. (There is evidence that epinephrine may be the drug of choice.)

Bronchospasm–Administer a $beta_2$-stimulating agent and/or a theophylline derivative.

DOSAGE: For all patients, DOSAGE MUST BE INDIVIDUALIZED.

For **angina pectoris,** usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 mg increments at 3 to 7 day intervals until optimum clinical response or pronounced slowing of the heart rate; usual maintenance dose is 80 to 240 mg q.d. (most patients respond to 160 mg or less daily). If treatment is to be discontinued, reduce dosage gradually over a period of 1 to 2 weeks (see WARNINGS).

For **hypertension,** usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 mg increments until optimum blood pressure reduction is achieved; usual maintenance dose is 80 to 320 mg q.d. (rarely, doses up to 640 mg may be needed).

Patients with renal failure require adjustment in dosing interval; see package insert for dosage in these patients.

For full prescribing information, consult package insert.

HOW SUPPLIED: In scored tablets containing 40, 80, 120, or 160 mg nadolol per tablet in bottles of 100 and 1000 tablets and in Unimatic® unit-dose packs of 100 tablets.

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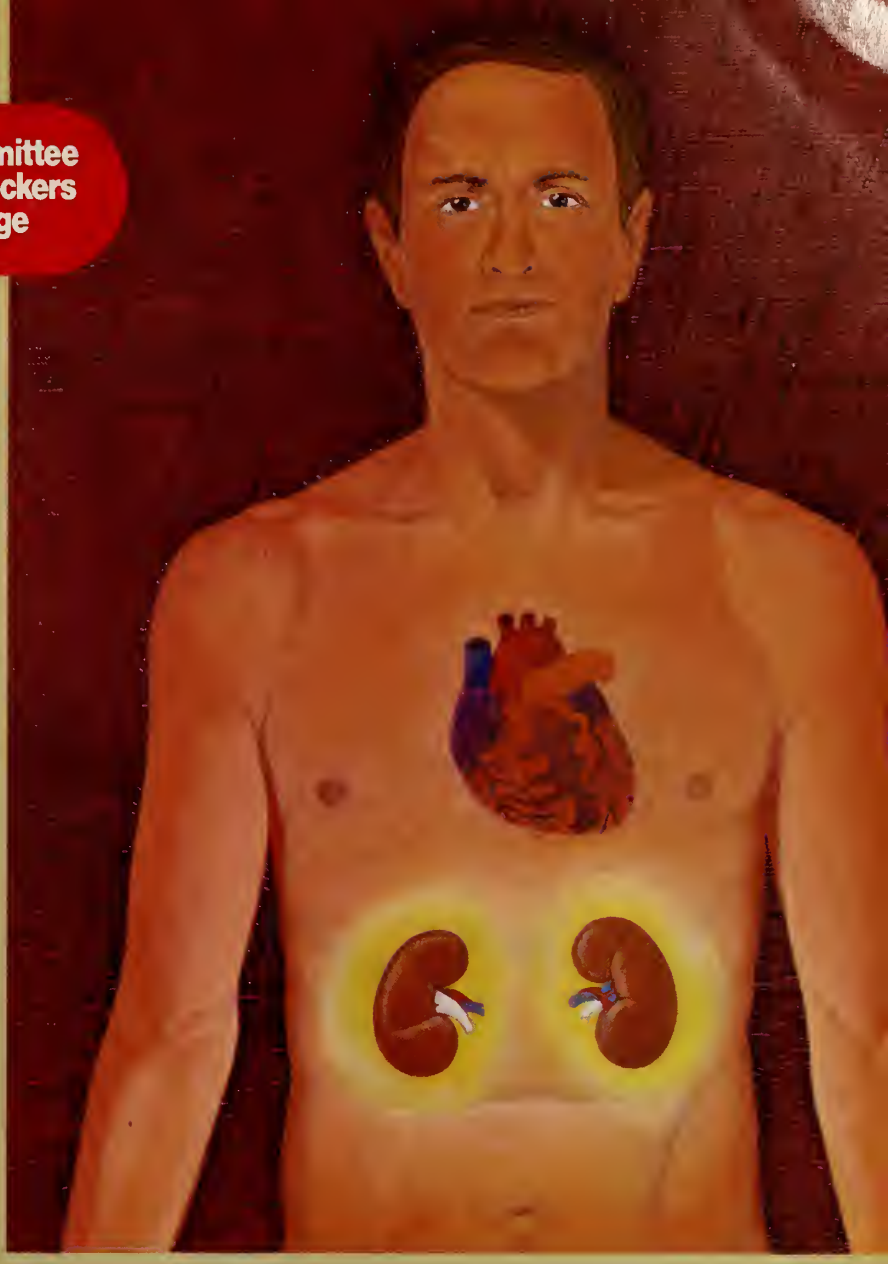

Effect on kidney

"...investigations suggest that the long-term use of nadolol, a long-acting nonselective agent, is associated with preserved renal function."[1]

"...the majority of investigators utilizing propranolol have reported decrements in RPF [renal plasma flow] and GFR [glomerular filtration rate]..."[1]

CORGARD® (nadolol tablets) should be used with caution in patients with impaired renal function.

Reference: 1. Epstein M, Oster JR: Beta-blockers and the kidney. Mineral Electrolyte Metab 8: 237-254, 1982.

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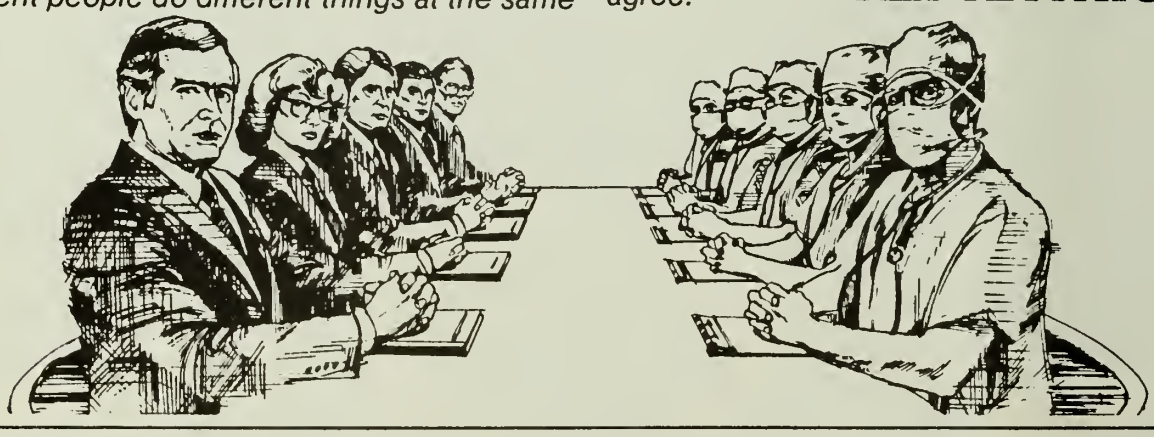

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ALLERGY AND IMMUNOLOGY

March 18-20—**Problem Areas in the Immunization Cycle.** American College of Preventitive Medicine at San Diego. Monday-Wednesday. Contact: National Council for International Health, 2100 Pennsylvania Ave. N.W., Ste. 740, Washington, DC 20073.

April 18-20—**Allergy and Immunology for the Practicing Physician.** UCSF. Thursday-Saturday. 18 hrs. Fee: $200.

ANESTHESIOLOGY

May 5-11—**12th Hawaiian Seminar on Clinical Anesthesia.** California Society of Anesthesiology at Sheraton Kauai Hotel, HA. Sunday-Saturday. 20 hrs. Contact: Education Programs Division, Calif. Society of Anesthesiology, 100 S. Ellsworth Ave., San Mateo, CA. (415) 348-1407.

May 17-22—**Anesthesiology Review Course.** UCSD at Vacation Village, San Diego. Friday-Wednesday. 38 hrs.

CANCER

March 22—**One Day Cancer Screening and Flexible Sigmoidoscopy Workshop.** Continuing Medical Education Associates at Holiday Inn Union Square, San Francisco. Friday. 7 hrs. Fee: $135. Contact: J. Shiller. CMEA, PO Box 84296, San Diego 92138.

March 24—**One Day Colon Cancer Screening and Flexible Sigmoidoscopy.** Continuing Medical Education Associates at Kona Kai Club, San Diego, Sunday. 7 hrs. Fee: $135. Contact: J. Shiller, CMEA, PO Box 84296, San Diego 92138.

April 6-8—**Diagnosis and Management of the Malignant Melanoma.** UCSF. Thursday-Saturday. 11 hrs. Fee: $250.

April 19—**Cancer Care.** Mt. Diablo Hospital Medical Center. Concord. Friday. 6 hrs. Fee: $100. Contact: Deborah Kolhede, Mt. Diablo Hospital and Medical Center, (415) 647-2359.

April 24—**Exploring the Future of Cancer Cures.** USC at Pasadena Hilton Hotel, Pasadena. Wednesday. Contact: Linda Richie-Walker (213) 224-7368.

CARDIOLOGY

March 16—**Cardiac Lecture Series: "Cardiovascular Trauma Texas Style."** Heart Institute of the Desert at Annenberg Center, Rancho Mirage. Saturday. 2 hrs. Contact: Eisenhower Medical Center, 39000 Bob Hope Dr., Rancho Mirage, CA 92270.

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 44 Gough Street, San Francisco 94103. (415) 863-5522.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Flora Harlee-Cordett, MS, MPH, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr., MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, ext. 2400.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 563-4321, ext. 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 497-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0328.

UCI: University of California, Irvine
Contact: E. R. Jennings, MD, Assistant Dean, University of California, Irvine, California College of Medicine, c/o UCI/CME Program, Memorial Hospital Medical Center, 2801 Atlantic Avenue, Long Beach 90801. (213) 595-3837, or (714) 856-5414, UCI Extension.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 452-3940.

UCSF: University of California, San Francisco
Contact: David S. Gullion, MD, Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 224-7051.

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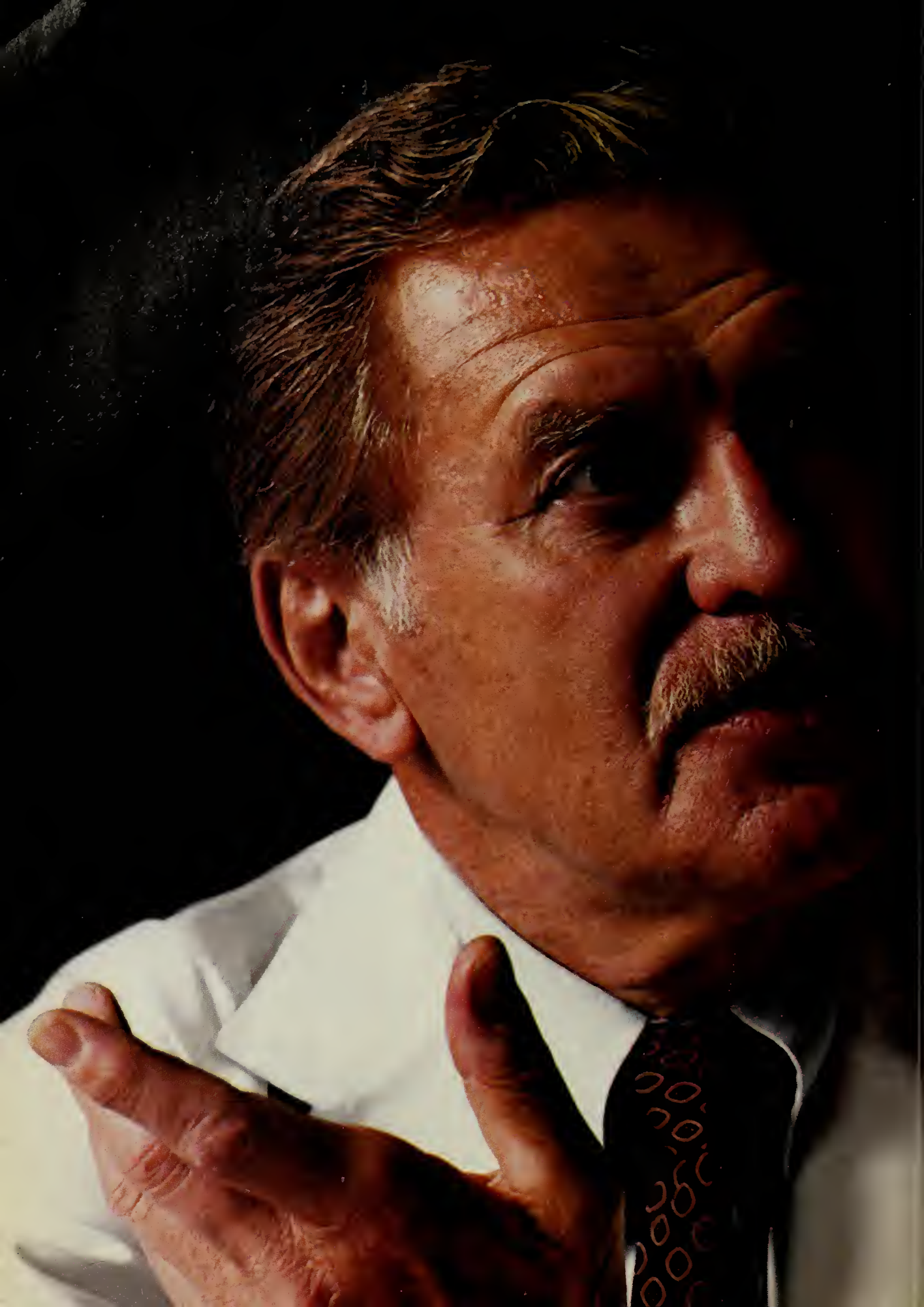


"When it comes to cardiovascular medicine, I like to know exactly what my patients are swallowing."

There are doctors who say that generic drugs have a place in their practice—but not necessarily in the treatment of serious or potentially life-threatening disease. And when they consider that the average patient pays only about 45¢ a day for INDERAL (propranolol HCl) Tablets, there's not much left to discuss.

When it's INDERAL Tablets you want for the treatment of hypertension, angina, arrhythmias, or post-MI patients, make sure you specify "Dispense As Written" (DAW), "Do Not Substitute," or whatever is required in your State. That way, you'll know exactly what your patients will get.

Please see next page for brief summary of prescribing information.

INDERAL® Tablets

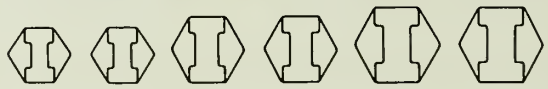
BRAND OF PROPRANOLOL HCl

Small price to pay.

"When it comes to cardiovascular medicine, I like to know exactly what my patients are swallowing."

INDERAL® Tablets

BRAND OF PROPRANOLOL HCl



10 mg 20 mg 40 mg 60 mg 80 mg 90 mg*

BRIEF SUMMARY (FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE CIRCULAR.)

INDERAL® (propranolol hydrochloride) Tablets

CONTRAINDICATIONS

INDERAL is contraindicated in 1) cardiogenic shock, 2) sinus bradycardia and greater than first degree block, 3) bronchial asthma, 4) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL.

WARNINGS

CARDIAC FAILURE. Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta blockade may precipitate more severe failure. Although beta blockers should be avoided in overt congestive heart failure, if necessary they can be used with close follow-up in patients with a history of failure who are well compensated and are receiving digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle.

IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta blockers can, in some cases, lead to cardiac failure. Therefore, at the first sign or symptom of heart failure, the patient should be digitalized and/or treated with diuretics, and the response observed closely; or INDERAL should be discontinued (gradually, if possible).

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following abrupt discontinuance of INDERAL therapy. Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced over at least a few weeks and the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)—PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

MAJOR SURGERY. The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

INDERAL, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in starting and maintaining the heartbeat has also been reported with beta blockers.

DIABETES AND HYPOGLYCEMIA. Beta-adrenergic blockade may prevent the appearance of certain premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia in labile insulin-dependent diabetes. In these patients, it may be more difficult to adjust the dosage of insulin.

THYROTOXICOSIS. Beta blockade may mask certain clinical signs of hyperthyroidism. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

PRECAUTIONS

General. Propranolol should be used with caution in patients with impaired hepatic or renal function. INDERAL is not indicated for the treatment of hypertensive emergencies.

Beta-adrenoreceptor blockade can cause reduction of intraocular pressure. Patients should be told that INDERAL (propranolol hydrochloride) may interfere with the glaucoma screening test. Withdrawal may lead to a return of increased intraocular pressure.

Clinical Laboratory Tests: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

DRUG INTERACTIONS. Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if INDERAL is administered. The added catecholamine-blocking action may produce an excessive reduction of resting sympathetic nervous activity which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility. Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In 18-month studies in both rats and mice, employing doses up to 150 mg/kg/day, there was no evidence of significant drug-induced toxicity. There were no drug-related tumorigenic effects at any of the dosage levels. Reproductive studies in animals did not show any impairment of fertility that was attributable to the drug.

Pregnancy. Pregnancy Category C. INDERAL has been shown to be embryotoxic in animal studies at doses about 10 times greater than the maximum recommended human dose.

There are no adequate and well-controlled studies in pregnant women. INDERAL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: INDERAL is excreted in human milk. Caution should be exercised when INDERAL is administered to a nursing woman.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Most adverse effects have been mild and transient and have rarely required the withdrawal of therapy.

Cardiovascular: bradycardia, congestive heart failure; intensification of AV block; hypotension, paresthesia of hands, thrombocytopenic purpura, arterial insufficiency, usually of the Raynaud type.

Central Nervous System: Lightheadedness; mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia; visual disturbances, hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Gastrointestinal: nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis.

Allergic: pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Respiratory: bronchospasm.

Hematologic: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Auto-Immune: In extremely rare instances, systemic lupus erythematosus has been reported.

Miscellaneous: alopecia, LE-like reactions, psoriasiform rashes, dry eyes, male impotence, and Peyronie's disease have been reported rarely. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been associated with propranolol.

*The appearance of INDERAL tablets is a registered trademark of Ayerst Laboratories.

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New York, N.Y. 10017

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March 18—**The Richard J. Bing Symposium IV—Cardiology 1985.** Huntington Memorial Hospital. Monday. 5.5 hrs. Fee: $35. Contact: Huntington Memorial Hospital, 100 Congress St., PO Box 7013, Pasadena 91109-7013.

March 22-24—**Cardiology for the Primary Care Physician.** UCSD at Palm Springs Spa Hotel. Friday-Sunday. 18 hrs.

March 23—**Reider Laser Symposium in Pulmonary Medicine.** UCI. Saturday. 7 hrs.

March 25-29—**Vascular and Pulmonary Diseases: Diagnosis & Management.** Medical Education Resources at Sheraton Maui, HI. 13 hrs. Fee: $275. Contact: Leslie Shaffer, Medical Education Resources, 5808 S. Rapp St., Ste 202, Littleton, CO 80120. (303) 798-9682.

March 29-31—**Vascular and Pulmonary Disease: Diagnosis and Management.** University of Colorado at Desert Inn, Las Vegas. Friday-Sunday. 13 hrs. Contact: Medical Education Resources, 5808 S. Rapp St., Ste. 202, Littleton, CO 80120. (800) 421-3756.

April 6—**Cardiac Lecture Series: The Ideal Conduit.** Heart Institute of the Desert at Annenberg Center, Rancho Mirage. Saturday. 2 hrs. Contact: Eisenhower Medical Center, 39000 Bob Hope Dr., Rancho Mirage 92270.

April 10-13—**1st Annual Program—Two Dimensional Echocardiography: Core Curriculum and Self-Assessment.** American College of Cardiology at Sheraton Harbor Island East, San Diego. Wednesday-Saturday. Contact: ACC, 9111 Old Georgetown Rd., Bethesda, MD 20814.

April 15-19—**ECG Interpretation and Arrhythmia Management.** International Medical Education Corp. at Marriott Hotel, Maui. Monday-Friday. 13 hrs. Fee: $295. Contact: IMEC, 64 Inverness Dr. East, Englewood, CO 80112.

April 20—**Cardiac Lecture Series: Advances in Research.** Heart Institute of the Desert at Annenberg Center, Rancho Mirage. Saturday. 2 hrs. Contact: Eisenhower Medical Center, 39000 Bob Hope Dr., Rancho Mirage 92270. (619) 568-2900.

April 26-28—**Coronary Artery Disease and Sudden Death: Primary and Secondary Prevention.** International Medical Education Corp. at Hyatt Union Square, San Francisco. Friday-Sunday. 13 hrs. Fee: $295. Contact: IMEC, 64 Inverness Dr. East, Englewood, CO 80112

April 26-28—**Vascular and Pulmonary Disease: Diagnosis and Management.** Medical Education Resources at Renaissance Hotel, San Francisco. Friday-Sunday. 13 hrs. Fee: $275. Contact: Leslie Shaffer, Medical Education Res., 5808 S. Rapp St., Ste 202, Littleton, CO 80120. (303) 798-9862.

May 10-12—**Coronary Artery Disease and Sudden Death: Primary and Secondary Prevention.** International Medical Education Corp. at Hyatt Islandia, San Diego. Friday-Sunday. Contact: IMEC, Div. of Postgraduate & Continuing Medical Education, 64 Inverness Dr. E., Englewood, CO 80112.

June 16-20—**Western Thoracic Surgical Association Annual Meeting** at Hyatt Lake Tahoe, Incline Village. Sunday-Thursday. Contact: WTSA, 13 Elm Street, Manchester, MA 01944. (617) 927-8330.

June 21-23—**Diagnosis and Management of the Acute M.I.** International Medical Education Corp. at Hyatt Regency, Lake Tahoe. Friday-Sunday. 13 hrs. Fee: $295. Contact: IMEC, 64 Inverness Dr. E., Englewood, CO 80112.

June 25-27—**Vascular and Pulmonary Disease: Diagnosis and Management.** Medical Education Resources at Balboa Bay Club, Newport Beach. Tuesday-Thursday. 13 hrs. Fee: $275. Contact: Mrs Leslie Shaffer, Medical Education Resources, 5808 S. Rapp Street, Ste. 202, Littleton, CO 80120. (303) 798-9682.

June 26-28—**Consultative Cardiology: Update in Diagnostic and Therapeutic Techniques.** American College of Cardiology at Westin South Coast Plaza, Costa Mesa. Wednesday-Friday. Contact: American College of Cardiology, 9111 Old Georgetown Rd., Bethesda, MD 20814.

June 28-30—**ECG Interpretation and Arrhythmia Management.** International Medical Education Corp. at Disneyland Hotel, Anaheim. Friday-Sunday. 13 hrs. Fee: $295. Contact: IMEC, 64 Inverness Dr. E, Englewood, CO 80112.

EMERGENCY MEDICINE

April 6-13—**Emergency Medicine—1985.** USC at Royal Lahaina Hotel, Maui. One week. 26.5 hrs. Fee: $495.

April 24-26—**Clinical Advances and Research Updates in Emergency Medicine.** UCSF at Holiday Inn—Golden Gateway, San Francisco. Wednesday-Friday. 15 hrs. Fee: $300.

May 6-10—**Postgraduate Institute for Emergency Physicians, Symposium I.** UCSD at Vacation Village, San Diego. One Week. 13-16 hrs. Fee: $200-675.

May 10-11—**2nd Annual Emergency Symposium.** Kaiser Permanente, Los Angeles at Century Plaza Hotel, Century City. Friday-Saturday. 10.5 hrs. Fee: $150. Contact: Dept. of Clinical Services, Southern Kaiser Permanente Medical Group, 4747 Sunset Blvd., Los Angeles 90024. (213) 667-4241.

May 13-19—**Update in Trauma.** University of Arizona at California Wine Country. Monday-Sunday.

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EDWARD PALMER, MD

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THOMAS G. COONEY, MD, and JAMES B. REULER, MD
From the Division of General Internal Medicine, Department of Medicine, The Oregon Health Sciences University, and Ambulatory Care and Medical Services, Veterans Administration Medical Center, Portland.

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From the Madigan Army Medical Center, Fort Lewis, Tacoma, Washington.

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LARRY MILLER, MD
At the time this article was written, Dr Miller was a Resident in Training in the Department of Internal Medicine, Evanston Hospital, Evanston, Illinois.

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LORING G. DALES, MD, and KENNETH W. KIZER, MD
Dr Dales is Medical Epidemiologist, Infectious Disease Section, California Department of Health Services, Berkeley. Dr Kizer is Deputy Director, Preventive Health Services, California Department of Health Services, Sacramento.

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NORBERT GOLDFIELD, MD, and LAWRENCE NEINSTEIN, MD
From the Departments of Internal Medicine and Pediatrics, University of Southern California School of Medicine, and the Division of Adolescent Medicine, Children's Hospital of Los Angeles. Dr Goldfield is now Medical Director, Cigna Corp, Hartford, Connecticut.

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IVAN A. D'CRUZ, MD, FACC, FRCP(Edin), MRCP(Lond)
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★ **Affiliated Clinical Investigation Societies: the Western Association of Physicians; the Western Society for Clinical Investigation; the Western Section, American Federation for Clinical Research; the Western Society for Pediatric Research; the Western Region, Society for Investigative Dermatology.**

BALANCED CALCIUM CHANNEL BLOCKADE!

CARDIZEM®
(diltiazem HCl)

balances potent coronary vasodilation with a low incidence of side effects

Low incidence of side effects
CARDIZEM® (diltiazem HCl) produces an incidence of adverse reactions not greater than that reported with placebo therapy, thus contributing to the patient's sense of well-being.

*Cardizem is indicated in the treatment of angina pectoris due to coronary artery spasm and in the management of chronic stable angina (classic effort-associated angina) in patients who cannot tolerate therapy with beta-blockers and/or nitrates or who remain symptomatic despite adequate doses of these agents.

References:

1. Strauss WE, McIntyre KM, Parisi AF, et al: Safety and efficacy of diltiazem hydrochloride for the treatment of stable angina pectoris: Report of a cooperative clinical trial. Am J Cardiol 49:560-566, 1982.
2. Pool PE, Seagren SC, Bonanno JA, et al: The treatment of exercise-inducible chronic stable angina with diltiazem: Effect on treadmill exercise. Chest 78 (July suppl):234-238, 1980.

Reduces angina attack frequency*
42% to 46% decrease reported in multicenter study.[1]

Increases exercise tolerance*
In Bruce exercise test,[2] control patients averaged 8.0 minutes to onset of pain; Cardizem patients averaged 9.8 minutes ($P<.005$).

CARDIZEM®
(diltiazem HCl)

THE BALANCED CALCIUM CHANNEL BLOCKER

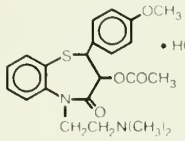
Please see full prescribing information on following page.

PROFESSIONAL USE INFORMATION

cardizem®
(diltiazem HCl)
30 mg and 60 mg tablets

DESCRIPTION

CARDIZEM® (diltiazem hydrochloride) is a calcium ion influx inhibitor (slow channel blocker or calcium antagonist). Chemically, diltiazem hydrochloride is 1,5-Benzothiazepin-4(5H)one,3-(acetyloxy) -5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-, monohydrochloride,(+) -cis- The chemical structure is:



Diltiazem hydrochloride is a white to off-white crystalline powder with a bitter taste It is soluble in water, methanol, and chloroform. It has a molecular weight of 450.98. Each tablet of CARDIZEM contains either 30 mg or 60 mg diltiazem hydrochloride for oral administration.

CLINICAL PHARMACOLOGY

The therapeutic benefits achieved with CARDIZEM are believed to be related to its ability to inhibit the influx of calcium ions during membrane depolarization of cardiac and vascular smooth muscle.

Mechanisms of Action. Although precise mechanisms of its antianginal actions are still being delineated, CARDIZEM is believed to act in the following ways:

1. Angina Due to Coronary Artery Spasm: CARDIZEM has been shown to be a potent dilator of coronary arteries both epicardial and subendocardial. Spontaneous and ergonovine-induced coronary artery spasm are inhibited by CARDIZEM.
2. Exertional Angina: CARDIZEM has been shown to produce increases in exercise tolerance, probably due to its ability to reduce myocardial oxygen demand. This is accomplished via reductions in heart rate and systemic blood pressure at submaximal and maximal exercise work loads.

In animal models, diltiazem interferes with the slow inward (depolarizing) current in excitable tissue. It causes excitation-contraction uncoupling in various myocardial tissues without changes in the configuration of the action potential. Diltiazem produces relaxation of coronary vascular smooth muscle and dilation of both large and small coronary arteries at drug levels which cause little or no negative inotropic effect. The resultant increases in coronary blood flow (epicardial and subendocardial) occur in ischemic and nonischemic models and are accompanied by dose-dependent decreases in systemic blood pressure and decreases in peripheral resistance.

Hemodynamic and Electrophysiologic Effects. Like other calcium antagonists, diltiazem decreases sinoatrial and atrioventricular conduction in isolated tissues and has a negative inotropic effect in isolated preparations. In the intact animal, prolongation of the AH interval can be seen at higher doses.

In man, diltiazem prevents spontaneous and ergonovine-provoked coronary artery spasm. It causes a decrease in peripheral vascular resistance and a modest fall in blood pressure and, in exercise tolerance studies in patients with ischemic heart disease, reduces the heart rate-blood pressure product for any given work load. Studies to date, primarily in patients with good ventricular function, have not revealed evidence of a negative inotropic effect, cardiac output, ejection fraction, and left ventricular end diastolic pressure have not been affected. There are as yet few data on the interaction of diltiazem and beta-blockers. Resting heart rate is usually unchanged or slightly reduced by diltiazem.

Intravenous diltiazem in doses of 20 mg prolongs AH conduction time and AV node functional and effective refractory periods approximately 20%. In a study involving single oral doses of 300 mg of CARDIZEM in six normal volunteers, the average maximum PR prolongation was 14% with no instances of greater than first-degree AV block. Diltiazem-associated prolongation of the AH interval is not more pronounced in patients with first-degree heart block. In patients with sick sinus syndrome, diltiazem significantly prolongs sinus cycle length (up to 50% in some cases).

Chronic oral administration of CARDIZEM in doses of up to 240 mg/day has resulted in small increases in PR interval, but has not usually produced abnormal prolongation. There were, however, three instances of second-degree AV block and one instance of third-degree AV block in a group of 959 chronically treated patients.

Pharmacokinetics and Metabolism. Diltiazem is absorbed from the tablet formulation to about 80% of a reference capsule and is subject to an extensive first-pass effect, giving an absolute bioavailability (compared to intravenous dosing) of about 40%. CARDIZEM undergoes extensive hepatic metabolism in which 2% to 4% of the unchanged drug appears in the urine. In vitro binding studies show CARDIZEM is 70% to 80% bound to plasma proteins. Competitive ligand binding studies have also shown CARDIZEM binding is not altered by therapeutic concentrations of digoxin, hydrochlorothiazide, phenylbutazone, propranolol, salicylic acid, or warfarin. Single oral doses of 30 to 120 mg of CARDIZEM result in detectable plasma levels within 30 to 60 minutes and peak plasma levels two to three hours after drug administration. The plasma elimination half-life following single or multiple drug administration is approximately 3.5 hours. Desacetyl diltiazem is also present in the plasma at levels of 10% to 20% of the parent drug and is 25% to 50% as potent a coronary vasodilator as diltiazem. Therapeutic blood levels of CARDIZEM appear to be in the range of 50 to 200 ng/ml. There is a departure from dose-linearity when single doses above 60 mg are given; a 120-mg dose gave blood levels three times that of the 60-mg dose. There is no information about the effect of renal or hepatic impairment on excretion or metabolism of diltiazem.

INOICATIONS ANO USAGE

1. **Angina Pectoris Due to Coronary Artery Spasm.** CARDIZEM is indicated in the treatment of angina pectoris due to coronary artery spasm. CARDIZEM has been shown effective in the treatment of spontaneous coronary artery spasm presenting as Prinzmetal's variant angina (resting angina with ST-segment elevation occurring during attacks).
2. **Chronic Stable Angina (Classic Effort-Associated Angina).** CARDIZEM is indicated in the management of chronic stable angina. CARDIZEM has been effective in controlled trials in reducing angina frequency and increasing exercise tolerance.

There are no controlled studies of the effectiveness of the concomitant use of diltiazem and beta-blockers or of the safety of this combination in patients with impaired ventricular function or conduction abnormalities.

CONTRAINOICATIONS

CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker, and (3) patients with hypotension (less than 90 mm Hg systolic).

WARNINGS

1. **Cardiac Conduction.** CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (six of 1243 patients for 0.48%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.
2. **Congestive Heart Failure.** Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). Experience with the use of CARDIZEM alone or in combination with beta-blockers in patients with impaired ventricular function is very limited. Caution should be exercised when using the drug in such patients.
3. **Hypotension.** Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.
4. **Acute Hepatic Injury.** In rare instances, patients receiving CARDIZEM have exhibited reversible acute hepatic injury as evidenced by moderate to extreme elevations of liver enzymes (See PRECAUTIONS and ADVERSE REACTIONS.)

PRECAUTIONS

General. CARDIZEM (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any new drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Drug Interaction. Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS).

Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers or digitalis is usually well tolerated. Available data are not sufficient, however, to predict the effects of concomitant treatment, particularly in patients with left ventricular dysfunction or cardiac conduction abnormalities. In healthy volunteers, diltiazem has been shown to increase serum digoxin levels up to 20%.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity There was also no mutagenic response in in vitro bacterial tests. No intrinsic effect on fertility was observed in rats.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

There are no well-controlled studies in pregnant women; therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when CARDIZEM is administered to a nursing woman if the drug's benefits are thought to outweigh its potential risks in this situation.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded

In domestic placebo-controlled trials, the incidence of adverse reactions reported during CARDIZEM therapy was not greater than that reported during placebo therapy

The following represent occurrences observed in clinical studies which can be at least reasonably associated with the pharmacology of calcium influx inhibition. In many cases, the relationship to CARDIZEM has not been established. The most common occurrences, as well as their frequency of presentation, are: edema (2.4%), headache (2.1%), nausea (1.9%), dizziness (1.5%), rash (1.3%), asthenia (1.2%), AV block (1.1%). In addition, the following events were reported infrequently (less than 1%) with the order of presentation corresponding to the relative frequency of occurrence.

Cardiovascular	Flushing, arrhythmia, hypotension, bradycardia, palpitations, congestive heart failure, syncope.
Nervous System:	Paresthesia, nervousness, somnolence, tremor, insomnia, hallucinations, and amnesia
Gastrointestinal.	Constipation, dyspepsia, diarrhea, vomiting, mild elevations of alkaline phosphatase, SGOT, SGPT, and LDH.
Dermatologic:	Pruritus, petechiae, urticaria, photosensitivity
Other.	Polyuria, nocturia.

The following additional experiences have been noted:

A patient with Prinzmetal's angina experiencing episodes of vasospastic angina developed periods of transient asymptomatic asystole approximately five hours after receiving a single 60-mg dose of CARDIZEM

The following postmarketing events have been reported infrequently in patients receiving CARDIZEM: erythema multiforme; leukopenia, and extreme elevations of alkaline phosphatase, SGOT, SGPT, LDH, and CPK. However, a definitive cause and effect between these events and CARDIZEM therapy is yet to be established.

OVERDOSAGE OR EXAGGERATEO RESPONSE

Overdosage experience with oral diltiazem has been limited. Single oral doses of 300 mg of CARDIZEM have been well tolerated by healthy volunteers. In the event of overdosage or exaggerated response, appropriate supportive measures should be employed in addition to gastric lavage. The following measures may be considered:

Bradycardia	Administer atropine (0.60 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.
High-Degree AV Block	Treat as for bradycardia above. Fixed high-degree AV block should be treated with cardiac pacing.
Cardiac Failure	Administer inotropic agents (isoproterenol, dopamine, or dobutamine) and diuretics.
Hypotension	Vasopressors (eg, dopamine or levarterenol bitartrate).

Actual treatment and dosage should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

The oral/LD_{50}'s in mice and rats range from 415 to 740 mg/kg and from 560 to 810 mg/kg, respectively. The intravenous LD_{50}'s in these species were 60 and 38 mg/kg, respectively. The oral LD_{50} in dogs is considered to be in excess of 50 mg/kg, while lethality was seen in monkeys at 360 mg/kg The toxic dose in man is not known but blood levels in excess of 800 ng/ml have not been associated with toxicity.

OOSAGE AND ADMINISTRATION

Exertional Angina Pectoris Due to Atherosclerotic Coronary Artery Disease or Angina Pectoris at Rest Due to Coronary Artery Spasm. Dosage must be adjusted to each patient's needs. Starting with 30 mg four times daily, before meals and at bedtime, dosage should be increased gradually (given in divided doses three or four times daily) at one- to two-day intervals until optimum response is obtained. Although individual patients may respond to any dosage level, the average optimum dosage range appears to be 180 to 240 mg/day. There are no available data concerning dosage requirements in patients with impaired renal or hepatic function. If the drug must be used in such patients, titration should be carried out with particular caution.

Concomitant Use With Other Antianginal Agents:

1. **Sublingual NTG** may be taken as required to abort acute anginal attacks during CARDIZEM therapy
2. **Prophylactic Nitrate Therapy**—CARDIZEM may be safely coadministered with short- and long-acting nitrates, but there have been no controlled studies to evaluate the antianginal effectiveness of this combination
3. **Beta-blockers.** (See WARNINGS and PRECAUTIONS.)

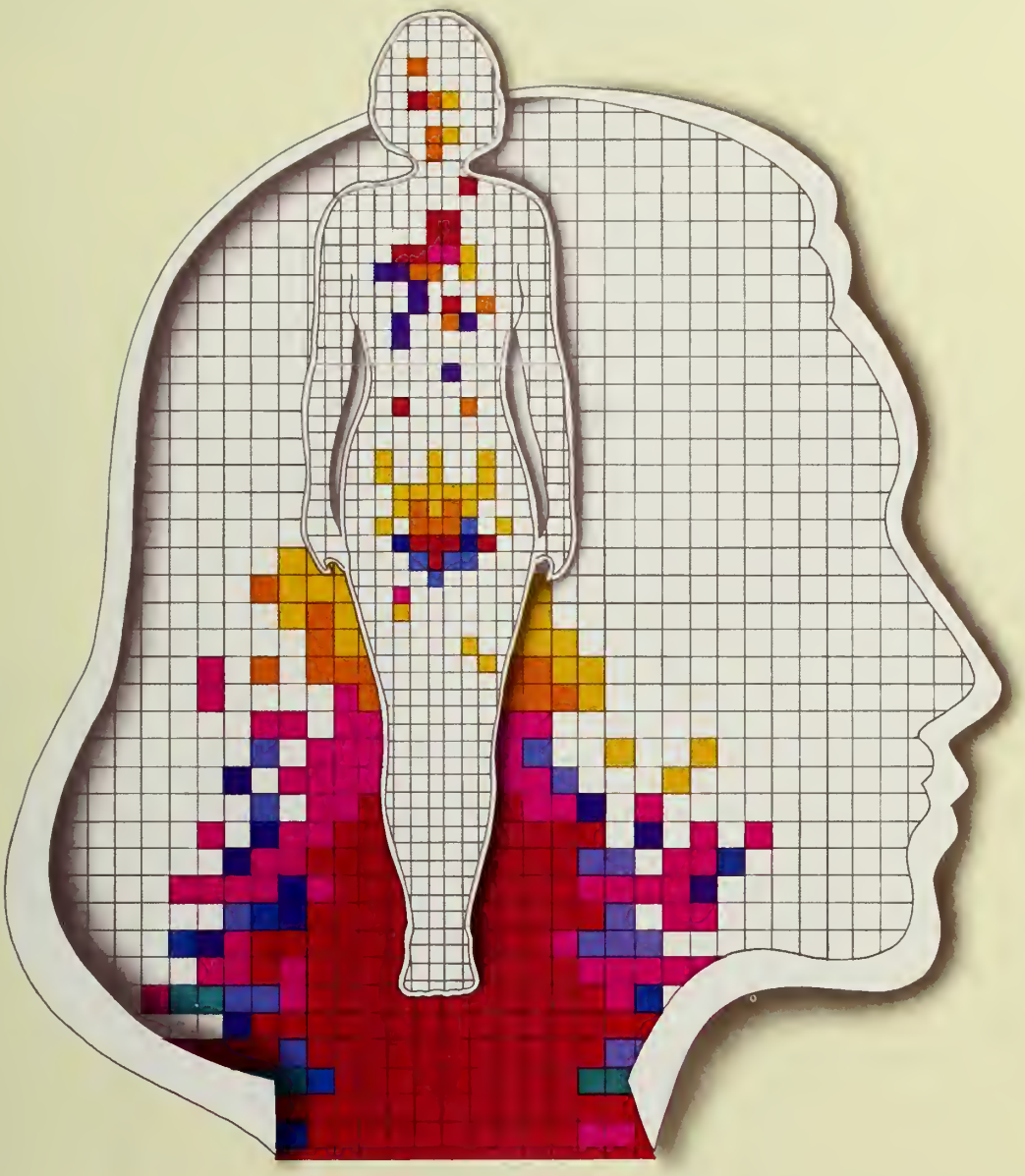
HOW SUPPLIEO

Cardizem 30-mg tablets are supplied in bottles of 100 (NDC 0088-1771-47) and in Unit Dose Identification Paks of 100 (NDC 0088-1771-49). Each green tablet is engraved with MARION on one side and 1771 engraved on the other. CARDIZEM 60-mg scored tablets are supplied in bottles of 100 (NDC 0088-1772-47) and in Unit Dose Identification Paks of 100 (NDC 0088-1772-49). Each yellow tablet is engraved with MARION on one side and 1772 on the other.

Issued 4/1/

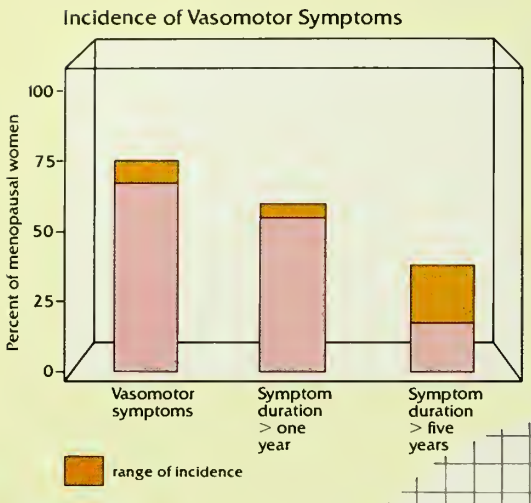
Another patient benefit product from

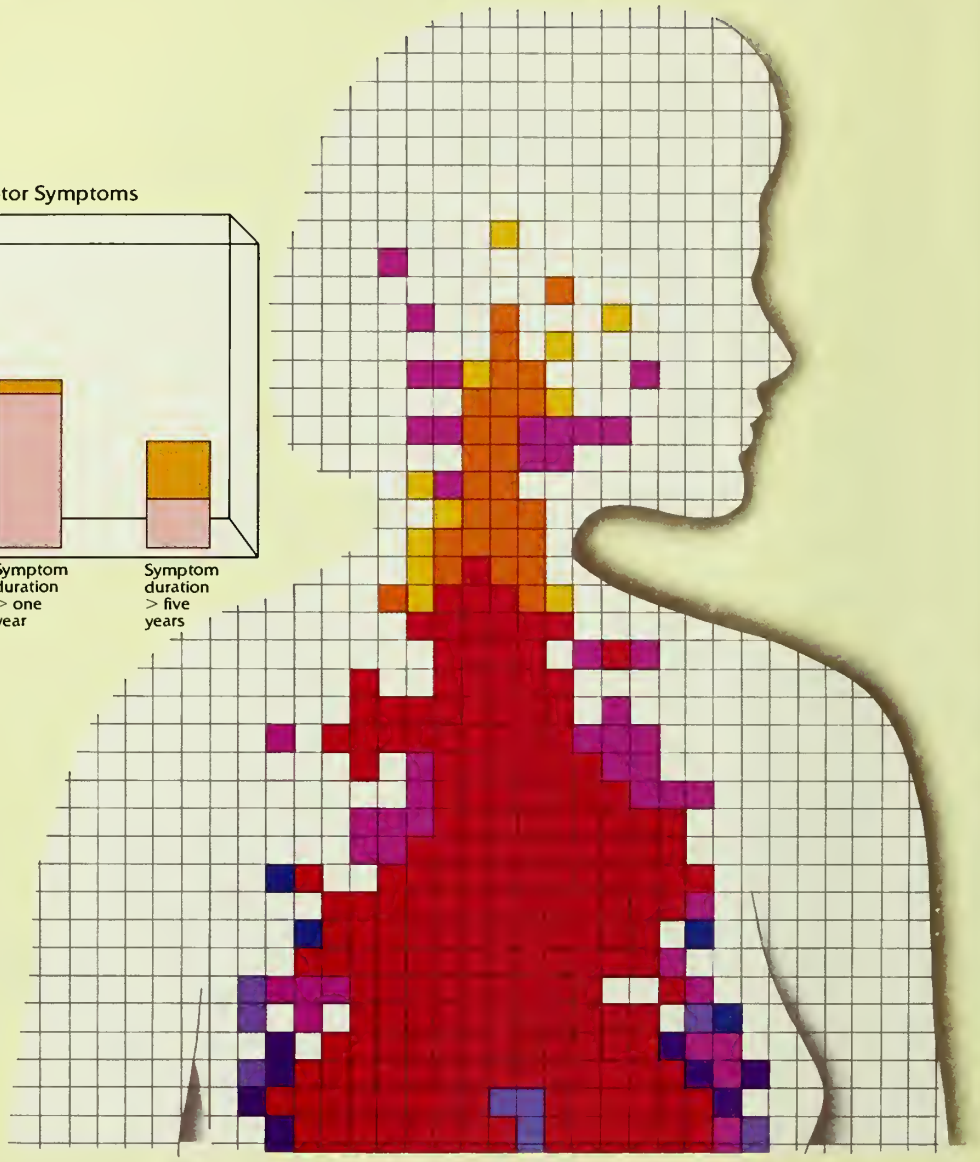
PHARMACEUTICAL DIVISION
MARION LABORATORIES, INC.
KANSAS CITY, MISSOURI 64137



THE ENDOCRINOLOGY OF AGING
Three profiles

VASOMOTOR SYMPTOMS THAT DEMAND INTERVENTION





PREMARIN RELIEVES MODERATE TO SEVERE VASOMOTOR SYMPTOMS

Vasomotor symptoms are the most common manifestation of the menopause, affecting up to 75% of menopausal women. Of these, 80% may suffer for more than a year and up to 50% for more than five years.[1] These symptoms can disrupt a woman's life by chronically interrupting sleep, resulting in anxiety and irritability.

In a study of postmenopausal women suffering severe episodes of cutaneous flushing, symptoms improved markedly after administration of estrogen[2]—the treatment of choice for moderate to severe vasomotor symptoms.[3] The estrogen of choice is PREMARIN, the most widely prescribed estrogen for over 40 years. PREMARIN (Conjugated Estrogens Tablets, U.S.P.) relieves moderate to severe vasomotor symptoms of the natural menopause, as well as the acute and often severe symptoms of surgical menopause.

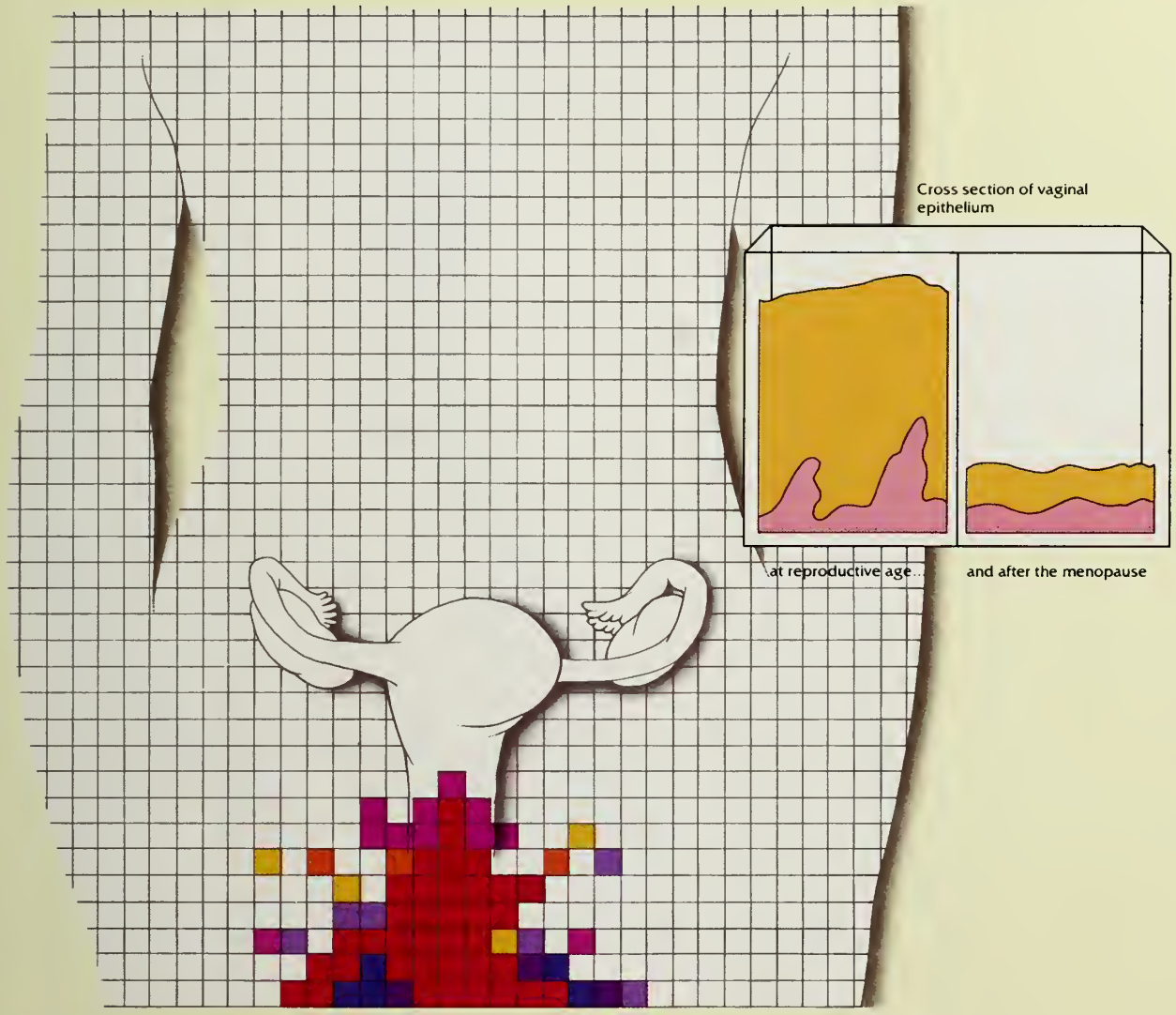
PREMARIN®

(CONJUGATED ESTROGENS TABLETS, U.S.P.)

0.3 mg 0.625 mg 0.9 mg 1.25 mg 2.5 mg

Please see last page for brief summary of full prescribing information.

VAGINAL ATROPHY THAT INTERFERES WITH SEXUALITY



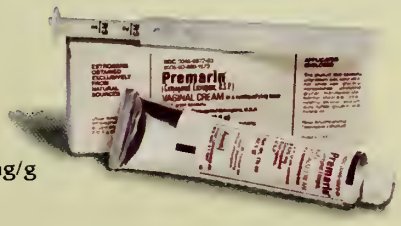
PREMARIN RESTORES THE VAGINAL ENVIRONMENT

In the postmenopausal woman, decreasing levels of estrogen can have devastating effects on a woman's sexual functioning. The pH of vaginal secretions rises, promoting the growth of contaminating organisms. The vaginal epithelium dries and thins, becoming susceptible to irritation, injury, and infection. Sexual relations may be difficult or impossible.

PREMARIN (Conjugated Estrogens, U.S.P.) Vaginal Cream focuses therapy at the site of the problem. Vaginal dryness is relieved, pH reverts to its normal acidity, and the epithelium thickens and becomes more resistant to injury and infection. With the vaginal environment returned to its premenopausal state, sexual function may improve.

PREMARIN®

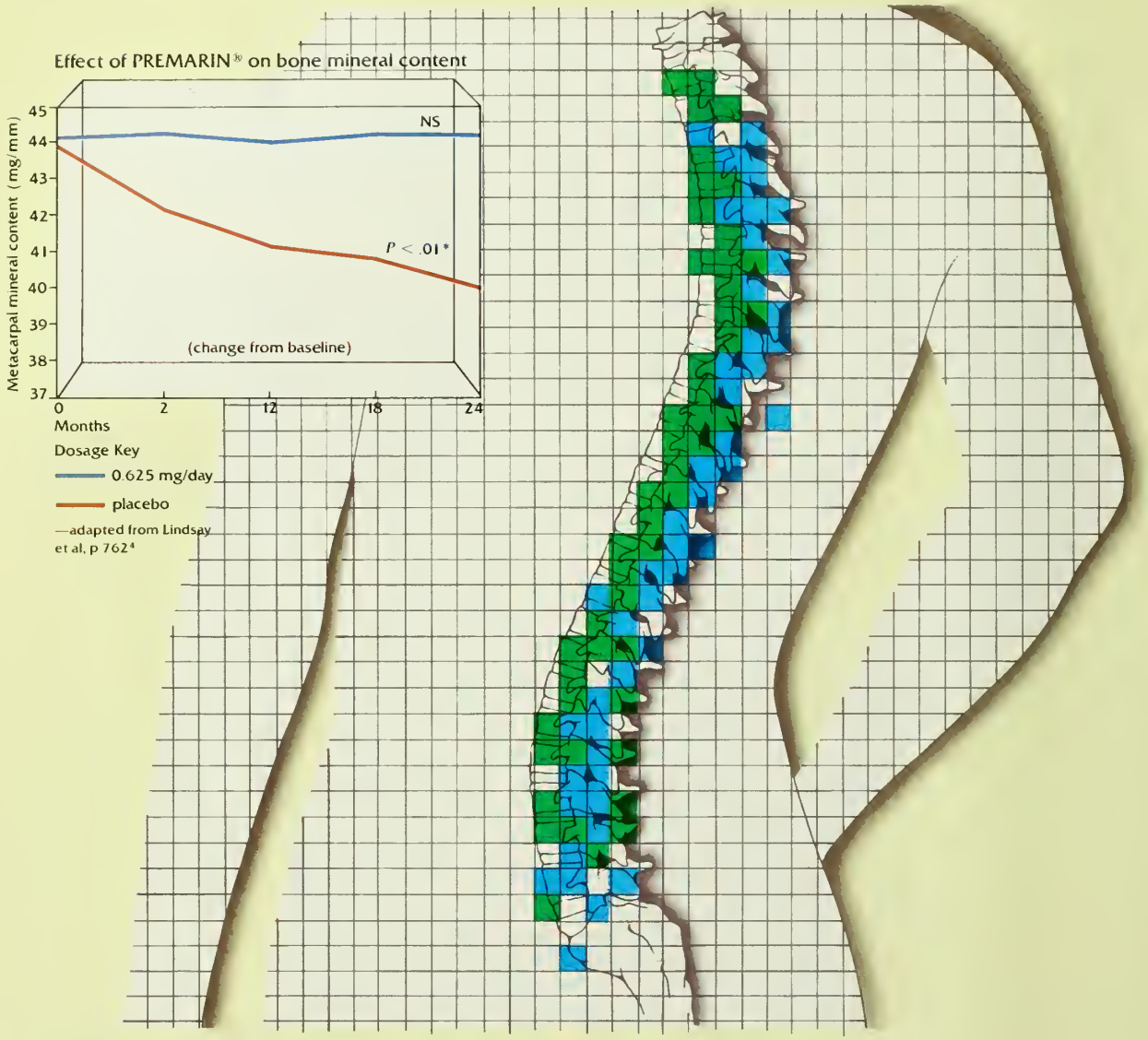
(CONJUGATED ESTROGENS, U.S.P.) Vaginal Cream



0.625 mg/g

Please see last page for brief summary of full prescribing information.

POSTMENOPAUSAL BONE LOSS THAT INCAPACITATES

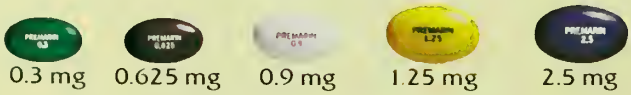


PREMARIN MAY HALT THE DISABLING COURSE OF OSTEOPOROSIS*

Osteoporosis has an enormous epidemiological impact: it affects 10 million American women, and 26% of all women over age 60.[5] The disease begins silently and progresses inexorably for 15 to 20 years, until disabling complications occur.[6]

To minimize osteoporotic damage, the condition must be detected early and treated promptly. For many patients, PREMARIN is optimal therapy for osteoporosis, as part of a comprehensive program that includes exercise, good nutrition, and calcium supplements. In a controlled study of postmenopausal and oophorectomized women, PREMARIN (Conjugated Estrogens Tablets, U.S.P.) doses of 0.625 mg/day prevented loss of metacarpal mineral content (see graph above).

PREMARIN®
(CONJUGATED ESTROGENS TABLETS, U.S.P.)



0.3 mg 0.625 mg 0.9 mg 1.25 mg 2.5 mg

*Conjugated Estrogens Tablets have been evaluated as probably effective for treating estrogen-deficiency-induced osteoporosis.

Please see last page for brief summary of full prescribing information.

BRIEF SUMMARY *(FOR FULL PRESCRIBING INFORMATION AND PATIENT INFORMATION, SEE PACKAGE CIRCULAR)*

PREMARIN® Brand of Conjugated Estrogens Tablets, U.S.P.
PREMARIN® Brand of Conjugated Estrogens, U.S.P. Vaginal Cream in a nonliquefying base

1. ESTROGENS HAVE BEEN REPORTED TO INCREASE THE RISK OF ENDOMETRIAL CARCINOMA.

Three independent case control studies have reported an increased risk of endometrial cancer in postmenopausal women exposed to exogenous estrogens for more than one year. This risk was independent of the other known risk factors for endometrial cancer. These studies are further supported by the finding that incidence rates of endometrial cancer have increased sharply since 1969 in eight different areas of the United States with population-based cancer reporting systems, an increase which may be related to the rapidly expanding use of estrogens during the last decade. The three case control studies reported that the risk of endometrial cancer in estrogen users was about 4.5 to 13.9 times greater than in nonusers. The risk appears to depend on both duration of treatment and on estrogen dose. In view of these findings, when estrogens are used for the treatment of menopausal symptoms, the lowest dose that will control symptoms should be utilized and medication should be discontinued as soon as possible. When prolonged treatment is medically indicated, the patient should be reassessed on at least a semiannual basis to determine the need for continued therapy. Although the evidence must be considered preliminary, one study suggests that cyclic administration of low doses of estrogen may carry less risk than continuous administration; it therefore appears prudent to utilize such a regimen. Close clinical surveillance of all women taking estrogens is important. In all cases of undiagnosed persistent or recurring abnormal vaginal bleeding, adequate diagnostic measures should be undertaken to rule out malignancy. There is no evidence at present that "natural" estrogens are more or less hazardous than "synthetic" estrogens at equiestrogenic doses.

2. ESTROGENS SHOULD NOT BE USED DURING PREGNANCY.

The use of female sex hormones, both estrogens and progestogens, during early pregnancy may seriously damage the offspring. It has been shown that females exposed in utero to diethylstilbestrol, a non-steroidal estrogen, have an increased risk of developing in later life a form of vaginal or cervical cancer that is ordinarily extremely rare. This risk has been estimated as not greater than 4 per 1000 exposures. Furthermore, a high percentage of such exposed women (from 30 to 90 percent) have been found to have vaginal adenosis, epithelial changes of the vagina and cervix. Although these changes are histologically benign, it is not known whether they are precursors of malignancy. Although similar data are not available with the use of other estrogens, it cannot be presumed they would not induce similar changes. Several reports suggest an association between intrauterine exposure to female sex hormones and congenital anomalies, including congenital heart defects and limb reduction defects. One case control study estimated a 4.7-fold increased risk of limb reduction defects in infants exposed in utero to sex hormones (oral contraceptives, hormone withdrawal tests for pregnancy, or attempted treatment for threatened abortion). Some of these exposures were very short and involved only a few days of treatment. The data suggest that the risk of limb reduction defects in exposed fetuses is somewhat less than 1 per 1000. In the past, female sex hormones have been used during pregnancy in an attempt to treat threatened or habitual abortion. There is considerable evidence that estrogens are ineffective for these indications, and there is no evidence from well controlled studies that progestogens are effective for these uses. If PREMARIN is used during pregnancy, or if the patient becomes pregnant while taking this drug, she should be apprised of the potential risks to the fetus, and the advisability of pregnancy continuation.

DESCRIPTION: PREMARIN (Conjugated Estrogens, U.S.P.) contains a mixture of estrogens, obtained exclusively from natural sources, blended to represent the average composition of material derived from pregnant mares' urine. It contains estrone, equilin, and 17α-dihydroequilin, together with smaller amounts of 17α-estradiol, equilenin, and 17α-dihydroequilenin as salts of their sulfate esters.

INDICATIONS: Based on a review of PREMARIN Tablets by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications for use as follows:

Effective: 1. Moderate to severe vasomotor symptoms associated with the menopause. (There is no evidence that estrogens are effective for nervous symptoms or depression without associated vasomotor symptoms, and they should not be used to treat such conditions.)

2. Atrophic vaginitis
3. Kraurosis vulvae
4. Female hypogonadism
5. Female castration
6. Primary ovarian failure
7. Breast cancer (for palliation only) in appropriately selected women and men with metastatic disease.
8. Prostatic carcinoma—palliative therapy of advanced disease.
9. Postpartum breast engorgement—Although estrogens have been widely used for the prevention of postpartum breast engorgement, controlled studies have demonstrated that the incidence of significant painful engorgement in patients not receiving such hormonal therapy is low and usually responsive to appropriate analgesic or other supportive therapy. Consequently, the benefit to be derived from estrogen therapy for this indication must be carefully weighed against the potential increased risk of puerperal thromboembolism associated with the use of large doses of estrogens.

PREMARIN HAS NOT BEEN SHOWN TO BE EFFECTIVE FOR ANY PURPOSE DURING PREGNANCY AND ITS USE MAY CAUSE SEVERE HARM TO THE FETUS (SEE BOXED WARNING).

"Probably" effective: For estrogen deficiency-induced osteoporosis, and only when used in conjunction with other important therapeutic measures such as diet, calcium, physiotherapy, and good general health-promoting measures. Final classification of this indication requires further investigation.

INDICATIONS: PREMARIN (Conjugated Estrogens, U.S.P.) Vaginal Cream is indicated in the treatment of atrophic vaginitis and kraurosis vulvae. PREMARIN Vaginal Cream HAS NOT BEEN SHOWN TO BE EFFECTIVE FOR ANY PURPOSE DURING PREGNANCY AND ITS USE MAY CAUSE SEVERE HARM TO THE FETUS (SEE BOXED WARNING).

CONTRAINDICATIONS: Estrogens should not be used in women (or men) with any of the following conditions: 1. Known or suspected cancer of the breast except in appropriately selected patients being treated for metastatic disease. 2. Known or suspected estrogen-dependent neoplasia. 3. Known or suspected pregnancy (See Boxed Warning). 4. Undiagnosed abnormal genital bleeding. 5. Active thrombophlebitis or thromboembolic disorders. 6. A past history of thrombophlebitis, thrombosis, or thromboembolic disorders associated with previous estrogen use (except when used in treatment of breast or prostatic malignancy).

WARNINGS: Long term continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, cervix, vagina, and liver. There are now reports that estrogens increase the risk of carcinoma of the endometrium in humans. (See Boxed Warning.) At the present time there is no satisfactory evidence that estrogens given to postmenopausal women increase the risk of cancer of the breast, although a recent study has raised this possibility. There is a need for caution in prescribing estrogens for women with a strong family history of breast cancer or who have breast nodules, fibrocystic disease, or abnormal mammograms. A recent study has reported a 2- to 3-fold increase in the risk of surgically confirmed gallbladder disease in women receiving postmenopausal estrogens.

Adverse effects of oral contraceptives may be expected at the larger doses of estrogen used to treat prostatic or breast cancer or postpartum breast engorgement; it has been shown that there is an increased risk of thrombosis in men receiving estrogens for prostatic cancer and women for postpartum breast engorgement. Users of oral contraceptives have an increased risk of diseases, such as thrombophlebitis, pulmonary embolism, stroke, and myocardial infarction. Cases of retinal thrombosis, mesenteric thrombosis, and optic neuritis have been reported in oral contraceptive users. An increased risk of postsurgery thromboembolic complications has also been reported in users of oral contraceptives. If feasible, estrogen should be discontinued at least 4 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization. Estrogens should not be used in persons with active thrombophlebitis, thromboembolic disorders, or in persons with a history of such disorders in association with estrogen use. They should be used with caution in patients with cerebral vascular or coronary artery disease. Large doses (5 mg conjugated estrogens per day), comparable to those used to treat cancer of the prostate and breast have been shown to increase the risk of nonfatal myocardial infarction, pulmonary embolism and thrombophlebitis. When doses of this size are used, any of the thromboembolic and thrombotic adverse effects should be considered a clear risk.

Benign hepatic adenomas should be considered in estrogen users having abdominal pain and tenderness, abdominal mass, or hypovolemic shock. Hepatocellular carcinoma has been reported in women taking estrogen-containing oral contraceptives. Increased blood pressure may occur with use of estrogens in the menopause and blood pressure should be monitored with estrogen use. A worsening of glucose tolerance has been observed in patients on estrogen-containing oral contraceptives. For this reason, diabetic patients should be carefully observed. Estrogens may lead to severe hypercalcemia in patients with breast cancer and bone metastases.

PRECAUTIONS: Physical examination and a complete medical and family history should be taken prior to the initiation of any estrogen therapy with special reference to blood pressure, breasts, abdomen, and pelvic organs, and should include a Papanicolau smear. As a general rule, estrogen should not be prescribed for longer than one year without another physical examination being performed. Conditions influenced by fluid retention such as asthma, epilepsy, migraine, and cardiac or renal dysfunction, require careful observation. Certain patients may develop manifestations of excessive estrogenic stimulation, such as abnormal or excessive uterine bleeding, mastodynia, etc. Prolonged administration of unopposed estrogen therapy has been reported to increase the risk of endometrial hyperplasia in some patients. Oral contraceptives appear to be associated with an increased incidence of mental depression. Patients with a history of depression should be carefully observed. Preexisting uterine leiomyomata may increase in size during estrogen use. The pathologist should be advised of estrogen therapy when relevant specimens are submitted. If jaundice develops in any patient receiving estrogen, the medication should be discontinued while the cause is investigated. Estrogens should be used with care in patients with impaired liver function, renal insufficiency, metabolic bone diseases associated with hypercalcemia, or in young patients in whom bone growth is not complete.

The following changes may be expected with larger doses of estrogen:

a. Increased sulfobromophthalein retention.
b. Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability.
c. Increased thyroid binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by PBI, T4 by column, or T4 by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG; free T4 concentration is unaltered.
d. Impaired glucose tolerance.
e. Decreased pregnanediol excretion.
f. Reduced response to metyrapone test.
g. Reduced serum folate concentration.
h. Increased serum triglyceride and phospholipid concentration.

As a general principle, the administration of any drug to nursing mothers should be done only when clearly necessary since many drugs are excreted in human milk.

ADVERSE REACTIONS: The following have been reported with estrogenic therapy, including oral contraceptives: breakthrough bleeding, spotting, change in menstrual flow; dysmenorrhea, premenstrual-like syndrome; amenorrhea during and after treatment; increase in size of uterine fibromyomata; vaginal candidiasis, change in cervical erosion and in degree of cervical secretion; cystitis-like syndrome; tenderness, enlargement, secretion (of breasts); nausea, vomiting, abdominal cramps, bloating; cholestatic jaundice; chloasma or melasma which may persist when drug is discontinued; erythema multiforme; erythema nodosum; hemorrhagic eruption; loss of scalp hair; hirsutism; steepening of corneal curvature; intolerance to contact lenses; headache, migraine, dizziness, mental depression, chorea; increase or decrease in weight; reduced carbohydrate tolerance; aggravation of porphyria, edema; changes in libido.

ACUTE OVERDOSAGE: May cause nausea, and withdrawal bleeding may occur in females.

DOSAGE AND ADMINISTRATION:

PREMARIN® Brand of Conjugated Estrogens Tablets, U.S.P.

1. *Given cyclically for short-term use only.* For treatment of moderate to severe *vasomotor* symptoms, atrophic vaginitis, or kraurosis vulvae associated with the menopause (0.3 to 1.25 mg or more daily).

The lowest dose that will control symptoms should be chosen and medication should be discontinued as promptly as possible.

Administration should be cyclic (*e.g.*, three weeks on and one week off).

Attempts to discontinue or taper medication should be made at three to six month intervals.

2. *Given cyclically:* Female hypogonadism. Female castration. Primary ovarian failure. Osteoporosis.

Female hypogonadism—2.5 to 7.5 mg daily, in divided doses for 20 days, followed by a rest period of 10 days' duration. If bleeding does not occur by the end of this period, the same dosage schedule is repeated. The number of courses of estrogen therapy necessary to produce bleeding may vary depending on the responsiveness of the endometrium.

If bleeding occurs before the end of the 10 day period, begin a 20 day estrogen-progestin cyclic regimen with PREMARIN (Conjugated Estrogens Tablets, U.S.P.), 2.5 to 7.5 mg daily in divided doses, for 20 days. During the last five days of estrogen therapy, give an oral progestin. If bleeding occurs before this regimen is concluded, therapy is discontinued and may be resumed on the fifth day of bleeding.

Female castration and primary ovarian failure—1.25 mg daily, cyclically. Adjust upward or downward according to response of the patient. For maintenance, adjust dosage to lowest level that will provide effective control.

Osteoporosis (to retard progression)—1.25 mg daily, cyclically.

3. *Given for a few days:* Prevention of postpartum breast engorgement—3.75 mg every four hours for five doses, or 1.25 mg every four hours for five days.

4. *Given chronically.* Inoperable progressing prostatic cancer—1.25 to 2.5 mg three times daily.

Inoperable progressing breast cancer in appropriately selected men and postmenopausal women—10 mg three times daily for a period of at least three months.

Patients with an intact uterus should be monitored for signs of endometrial cancer and appropriate measures taken to rule out malignancy in the event of persistent or recurring abnormal vaginal bleeding.

PREMARIN® Brand of Conjugated Estrogens, U.S.P. Vaginal Cream

Given cyclically for short-term use only. For treatment of atrophic vaginitis or kraurosis vulvae.

The lowest dose that will control symptoms should be chosen and medication should be discontinued as promptly as possible.

Administration should be cyclic (*e.g.*, three weeks on and one week off).

Attempts to discontinue or taper medication should be made at three to six month intervals.

Usual dosage range: 2 to 4 g daily, intravaginally or topically, depending on the severity of the condition.

Treated patients with an intact uterus should be monitored closely for signs of endometrial cancer and appropriate diagnostic measures should be taken to rule out malignancy in the event of persistent or recurring abnormal vaginal bleeding.

HOW SUPPLIED: PREMARIN (Conjugated Estrogens Tablets, U.S.P.). No. 865—Each *purple* tablet contains 2.5 mg in bottles of 100 and 1,000. No. 866—Each *yellow* tablet contains 1.25 mg in bottles of 100 and 1,000. Also in Cycle Pack of 21 and in unit dose package of 100. No. 864—Each *white* tablet contains 0.9 mg in bottles of 100. Also in Cycle Pack of 21. No. 867—Each *maroon* tablet contains 0.625 mg in bottles of 100 and 1,000. Also in Cycle Pack of 21 and unit dose package of 100. No. 868—Each *green* tablet contains 0.3 mg in bottles of 100 and 1,000. The appearance of these tablets is a trademark of Ayerst Laboratories.

PREMARIN (Conjugated Estrogens, U.S.P.) Vaginal Cream—No. 872—Each gram contains 0.625 mg Conjugated Estrogens, U.S.P. (Also contains cetyl esters wax, cetyl alcohol, white wax, glyceryl monostearate, propylene glycol monostearate, methyl stearate, phenylethyl alcohol, sodium lauryl sulfate, glycerin, and mineral oil.)

Combination package: Each contains Net Wt. 1½ oz. (42.5 g) tube with one calibrated plastic applicator.

Also Available—Refill package: Each contains Net Wt. 1½ oz. (42.5 g) tube.

4340/285

References: 1. Judd HL: After the menopause. *Transition* 1983;1:19-30. **2.** Erlik Y, Tataryn IV, Meldrum DR, et al: Association of waking episodes with menopausal hot flushes. *JAMA* 1981;245:1741-1744. **3.** Meldrum DR: The pathophysiology of postmenopausal symptoms. *Sem Reprod Endocrinol* 1983;1(February):11-17. **4.** Lindsay R, Hart DM, Clark DM: The minimum effective dose of estrogen for prevention of postmenopausal bone loss. *Obstet Gynecol* 1984;63:759-763. **5.** Katz WA: *Rheumatic Diseases: Diagnosis and Management*. Philadelphia, JB Lippincott Co, 1977, p 672. **6.** Reese WD: A better way to screen for osteoporosis. *Contemp Ob/Gyn* 1983;22(November):116-131.

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Clinical Investigation—Papers that authors wish considered for the Clinical Investigation section should be so designated in the transmittal letter.

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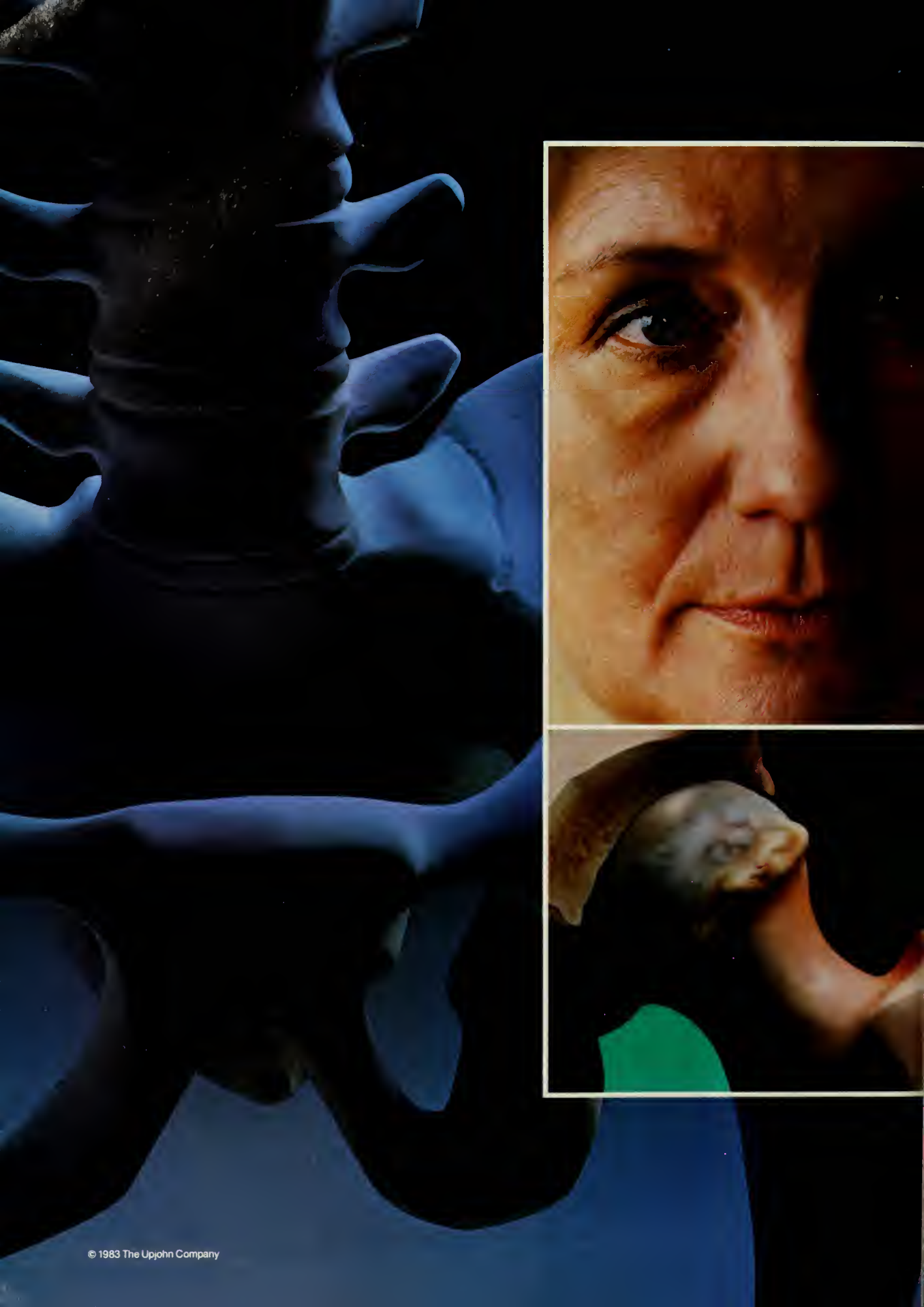

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Arthritis pain after 50

Age is no barrier to the benefits of Motrin 600 mg tablets

The pain-relieving power of *Motrin* 600 mg tablets is welcome at any age. The advantages of *Motrin* become more important as patients grow older.

Advanced age has little or no influence on the pharmacokinetics of *Motrin.*

Motrin is as effective as indomethacin in relieving arthritis pain and inflammation. *Motrin* causes significantly fewer CNS effects and about half as many GI complaints as indomethacin.

Motrin relieves pain as effectively as a combination of aspirin 650 mg plus codeine 60 mg, as documented in analgesia studies.

Motrin has no significant effect on clotting factors in patients on coumarin-type anticoagulants in controlled studies. *Motrin* should be used with caution in persons with intrinsic coagulation defects and in those on anticoagulant therapy.

Motrin is rapidly metabolized and does not accumulate. *Motrin* provides better control of therapy, rapid response to dosage adjustment, and permits tailoring dosage to each patient's needs.

New: The Motrin Patient Brochure
An easy-to-read booklet, provided to physicians, that helps patients understand their arthritis therapy... encourages their cooperation.

Helping you to help your patients—
Ask your Upjohn Representative for a complimentary supply.

The confidence that comes from experience...good reason to prescribe

Motrin® 600 mg TABLETS (ibuprofen)

One tablet t.i.d.

Please turn page for a brief summary of prescribing information.

Upjohn The Upjohn Company
Kalamazoo, Michigan 49001

Motrin® Tablets (ibuprofen)

Contraindications: Anaphylactoid reactions have occurred in individuals hypersensitive to *Motrin* Tablets or with the syndrome of nasal polyps, angioedema and bronchospastic reactivity to aspirin, iodides, or other nonsteroidal anti-inflammatory agents.

Warnings: Peptic ulceration and GI bleeding, sometimes severe, have been reported. Ulceration, perforation and bleeding may end fatally. An association has not been established. Use *Motrin* Tablets under close supervision in patients with a history of upper gastrointestinal tract disease, after consulting ADVERSE REACTIONS. In patients with active peptic ulcer and active rheumatoid arthritis, try nonulcerogenic drugs, such as gold. If *Motrin* Tablets are used, observe the patient closely for signs of ulcer perforation or GI bleeding.

Chronic studies in rats and monkeys have shown mild renal toxicity with papillary edema and necrosis. Renal papillary necrosis has rarely been shown in humans treated with *Motrin* Tablets.

Precautions: Blurred and/or diminished vision, scotomata, and/or changes in color vision have been reported. If these develop, discontinue *Motrin* Tablets and the patient should have an ophthalmologic examination, including central visual fields and color vision testing.

Fluid retention and edema have been associated with *Motrin* Tablets; use with caution in patients with a history of cardiac decompensation or hypertension. In patients with renal impairment, reduced dosage may be necessary. Prospective studies of *Motrin* Tablets safety in patients with chronic renal failure have not been done.

Motrin Tablets can inhibit **platelet aggregation** and prolong bleeding time. Use with caution in persons with intrinsic coagulation defects and on anticoagulant therapy.

Patients should report signs or symptoms of **gastrointestinal ulceration** or bleeding, skin rash, weight gain, or edema.

Patients on prolonged **corticosteroid therapy** should have therapy tapered slowly when *Motrin* Tablets are added.

The antipyretic, anti-inflammatory activity of *Motrin* Tablets may mask inflammation and fever.

As with other nonsteroidal anti-inflammatory drugs, borderline elevations of liver tests may occur in up to 15% of patients. These abnormalities may progress, may remain essentially unchanged, or may be transient with continued therapy. Meaningful elevations of SGPT or SGOT (AST) occurred in controlled clinical trials in less than 1% of patients. Severe hepatic reactions, including jaundice and cases of fatal hepatitis, have been reported with ibuprofen as with other nonsteroidal anti-inflammatory drugs. If liver disease develops or if systemic manifestations occur (e.g. eosinophilia, rash, etc.), *Motrin* should be discontinued.

Drug interactions. *Aspirin:* used concomitantly may decrease *Motrin* blood levels.

Coumarin: bleeding has been reported in patients taking *Motrin* and coumarin.

Pregnancy and nursing mothers: *Motrin* should not be taken during pregnancy or by nursing mothers.

Adverse Reactions: The most frequent type of adverse reaction occurring with *Motrin* is gastrointestinal of which one or more occurred in 4% to 16% of the patients.

Incidence Greater than 1% (but less than 3%)–Probable Causal Relationship

Gastrointestinal: Nausea,* epigastric pain,* heartburn,* diarrhea, abdominal distress, nausea and vomiting, indigestion, constipation, abdominal cramps or pain, fullness of GI tract (bloating and flatulence); **Central Nervous System:** Dizziness,* headache, nervousness; **Dermatologic:** Rash* (including maculopapular type), pruritus; **Special Senses:** Tinnitus; **Metabolic/Endocrine:** Decreased appetite; **Cardiovascular:** Edema, fluid retention (generally responds promptly to drug discontinuation; see PRECAUTIONS).

Incidence less than 1%–Probable Causal Relationship**

Gastrointestinal: Gastric or duodenal ulcer with bleeding and/or perforation, gastrointestinal hemorrhage, melena, gastritis, hepatitis, jaundice, abnormal liver function tests; **Central Nervous System:** Depression, insomnia, confusion, emotional lability, somnolence, aseptic meningitis with fever and coma; **Dermatologic:** Vesiculobullous eruptions, urticaria, erythema multiforme, Stevens-Johnson syndrome, alopecia; **Special Senses:** Hearing loss, amblyopia (blurred and/or diminished vision, scotomata, and/or changes in color vision) (see PRECAUTIONS); **Hematologic:** Neutropenia, agranulocytosis, aplastic anemia, hemolytic anemia (sometimes Coombs positive), thrombocytopenia with or without purpura, eosinophilia, decreases in hemoglobin and hematocrit; **Cardiovascular:** Congestive heart failure in patients with marginal cardiac function, elevated blood pressure, palpitations; **Allergic:** Syndrome of abdominal pain, fever, chills, nausea and vomiting; anaphylaxis; bronchospasm (see CONTRAINDICATIONS); **Renal:** Acute renal failure in patients with pre-existing significantly impaired renal function, decreased creatinine clearance, polyuria, azotemia, cystitis, hematuria; **Miscellaneous:** Dry eyes and mouth, gingival ulcer, rhinitis.

Incidence less than 1%–Causal Relationship Unknown**

Gastrointestinal: Pancreatitis; **Central Nervous System:** Paresthesias, hallucinations, dream abnormalities, pseudotumor cerebri; **Dermatologic:** Toxic epidermal necrolysis, photoallergic skin reactions; **Special Senses:** Conjunctivitis, diplopia, optic neuritis; **Hematologic:** Bleeding episodes (e.g., epistaxis, menorrhagia); **Metabolic/Endocrine:** Gynecomastia, hypoglycemic reaction; **Cardiovascular:** Arrhythmias (sinus tachycardia, sinus bradycardia); **Allergic:** Serum sickness, lupus erythematosus syndrome, Henoch-Schönlein vasculitis; **Renal:** Renal papillary necrosis.

*Reactions occurring in 3% to 9% of patients treated with *Motrin*. (Those reactions occurring in less than 3% of the patients are unmarked.)

**Reactions are classified under *"Probable Causal Relationship (PCR)"* if there has been one positive rechallenge or if three or more cases occur which might be causally related. Reactions are classified under *"Causal Relationship Unknown"* if seven or more events have been reported but the criteria for PCR have not been met.

Overdosage: In cases of acute overdosage, the stomach should be emptied. The drug is acidic and excreted in the urine so alkaline diuresis may be beneficial.

Dosage and Administration: Rheumatoid arthritis and osteoarthritis. Suggested dosage is 300, 400, or 600 mg t.i.d. or q.i.d. Do not exceed 2400 mg per day. Mild to moderate pain: 400 mg every 4 to 6 hours as necessary.

Caution: Federal law prohibits dispensing without prescription.

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MED B-7-S

J-3253 June 1983

Upjohn

CONTINUING MEDICAL EDUCATION

(Continued from Page 309)

24 hrs. Contact: Richard Paris, MD, PO Box 209, Sun Valley, ID 83353. (208) 788-4995.

May 15-19—**Wound Management Workshop.** UCSD at Holiday Inn at the Embarcadero, San Diego. Monday-Friday. 19 hrs.

May 20-24—**Topics in Emergency Medicine.** UCSF at Sheraton at Fishermans Wharf, San Francisco. Monday-Friday. 33 hrs. Fee: $400.

June 24-28—**Postgraduate Institute for Emerg. Physicians, Symposium 111.** UCSD at Hanalei Hotel, San Diego. Monday-Friday. 13-36 hrs. Fee: $200-675.

June 27-30—**Update in Emergency Medicine.** Mercy Medical Center, Redding at Salmon River (Whitewater rafting trip). Thursday-Sunday. 10 hrs. Fee: $125. Contact: Shelly Underwood, Mercy Medical Center, Redding, PO Box 6009, Redding, CA 96099-6009. (916) 243-2121.

INTERNAL MEDICINE

March 15-16—**Reider Laser Symposium in Urology.** UCI. Friday-Saturday. 14 hrs.

March 18—**Reider Laser Symposium in Gastroenterology.** UCI. Monday. 7 hrs.

March 18-19—**Reider Laser Symposium in Neurosurgery.** UCI. Monday-Tuesday. 12 hrs.

March 18-20—**Gastroenterology Course.** UCSF at Yosemite. Monday-Wednesday. Contact: UCSF.

March 19-22—**Internal Medicine Update.** UCD at Red Lion Motor Inn, Sacramento. Tuesday-Friday.

March 23—**Reider Laser Symposium in Head, Neck, and Facial Surgery.** UCI. Saturday. 7 hrs.

April 12-13—**Update in Gastroenterology.** Annenberg Center for Health Sciences, at Rancho Mirage. Friday-Saturday. Contact: Annenberg Center for Health Sciences, Eisenhower Medical Center, 39000 Bob Hope Dr., Rancho Mirage 92270. (800) 621-7322.

April 22-24—**Advances in Infectious Diseases.** UCSF at Mark Hopkins Hotel, San Francisco. Monday-Wednesday. Fee: $325.

April 24—**Thyroid '85.** The Hospital of the Good Samaritan at Hyatt Regency Hotel, Los Angeles. Wednesday. 6 hrs. Contact: Dolores Gay, 616 South Witmer St., Los Angeles 90017. (213) 977-2352.

April 27—**Nephrology.** UCSF at Fresno. Saturday.

May 8—**Gastroenterology: G.I. Bleeding.** LLU. Wednesday. 4 hrs.

May 13-17—**Advances in Internal Medicine.** UCSF. Wednesday-Sunday. Fee: $465.

(Continued on Page 324)

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DISTINCTIVE DESIGN 0.5, 1.0 and 2.0 mg

Brief Summary of Prescribing Information.

Indications and Usage: Management of anxiety disorders or short-term relief of symptoms of anxiety or anxiety associated with depressive symptoms. Anxiety or tension associated with stress of everyday life usually does not require treatment with an anxiolytic.

Effectiveness in long-term use, i.e., more than 4 months, has not been assessed by systematic clinical studies. Reassess periodically usefulness of the drug for the individual patient.

Contraindications: Known sensitivity to benzodiazepines or acute narrow-angle glaucoma.

Warnings: Not recommended in primary depressive disorders or psychoses. As with all CNS-acting drugs, warn patients not to operate machinery or motor vehicles, and of diminished tolerance for alcohol and other CNS depressants.

Physical and Psychological Dependence: Withdrawal symptoms like those noted with barbiturates and alcohol have occurred following abrupt discontinuance of benzodiazepines (including convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Addiction-prone individuals, e.g. drug addicts and alcoholics, should be under careful surveillance when on benzodiazepines because of their predisposition to habituation and dependence. Withdrawal symptoms have also been reported following abrupt discontinuance of benzodiazepines taken continuously at therapeutic levels for several months.

Precautions: In depression accompanying anxiety, consider possibility for suicide.

For elderly or debilitated patients, initial daily dosage should not exceed 2mg to avoid oversedation. Terminate dosage gradually since abrupt withdrawal of any antianxiety agent may result in symptoms like those being treated: anxiety, agitation, irritability, tension, insomnia and occasional convulsions. Observe usual precautions with impaired renal or hepatic function. Where gastrointestinal or cardiovascular disorders coexist with anxiety, note that lorazepam has not been shown of significant benefit in treating gastrointestinal or cardiovascular component. Esophageal dilation occurred in rats treated with lorazepam for more than 1 year at 6mg/kg/day. No effect dose was 1.25mg/kg/day (about 6 times maximum human therapeutic dose of 10mg/day). Effect was reversible only when treatment was withdrawn within 2 months of first observation. Clinical significance is unknown; but use of lorazepam for prolonged periods and in geriatrics requires caution and frequent monitoring for symptoms of upper G.I. disease. Safety and effectiveness in children under 12 years have not been established.

ESSENTIAL LABORATORY TESTS: Some patients have developed leukopenia; some have had elevations of LDH. As with other benzodiazepines, periodic blood counts and liver function tests are recommended during long-term therapy.

CLINICALLY SIGNIFICANT DRUG INTERACTIONS: Benzodiazepines produce CNS depressant effects when administered with such medications as barbiturates or alcohol.

CARCINOGENESIS AND MUTAGENESIS: No evidence of carcinogenic potential emerged in rats during an 18-month study. No studies regarding mutagenesis have been performed.

PREGNANCY: Reproductive studies were performed in mice, rats, and 2 strains of rabbits. Occasional anomalies (reduction of tarsals, tibia, metatarsals, malrotated limbs, gastroschisis, malformed skull and microphthalmia) were seen in drug-treated rabbits without relationship to dosage. Although all these anomalies were not present in the concurrent control group, they have been reported to occur randomly in historical controls. At 40mg/kg and higher, there was evidence of fetal resorption and increased fetal loss in rabbits which was not seen at lower doses. Clinical significance of these findings is not known. However, increased risk of congenital malformations associated with use of minor tranquilizers (chlordiazepoxide, diazepam and meprobamate) during first trimester of pregnancy has been suggested in several studies. Because use of these drugs is rarely a matter of urgency, use of lorazepam during this period should almost always be avoided. Possibility that a woman of child-bearing potential may be pregnant at institution of therapy should be considered. Advise patients if they become pregnant to communicate with their physician about desirability of discontinuing the drug. In humans, blood levels from umbilical cord blood indicate placental transfer of lorazepam and its glucuronide.

NURSING MOTHERS: It is not known if oral lorazepam is excreted in human milk like other benzodiazepines. As a general rule, nursing should not be undertaken while on a drug since many drugs are excreted in milk.

Adverse Reactions, if they occur, are usually observed at beginning of therapy and generally disappear on continued medication or on decreasing dose. In a sample of about 3,500 anxious patients, most frequent adverse reaction is sedation (15.9%), followed by dizziness (6.9%), weakness (4.2%) and unsteadiness (3.4%). Less frequent are disorientation, depression, nausea, change in appetite, headache, sleep disturbance, agitation, dermatological symptoms, eye function disturbance, various gastrointestinal symptoms and autonomic manifestations. Incidence of sedation and unsteadiness increased with age. Small decreases in blood pressure have been noted but are not clinically significant, probably being related to relief of anxiety.

Transient amnesia or memory impairment has been reported in association with the use of benzodiazepines.

Overdosage: In management of overdosage with any drug, bear in mind multiple agents may have been taken. Manifestations of overdosage include somnolence, confusion and coma. Induce vomiting and/or undertake gastric lavage followed by general supportive care, monitoring vital signs and close observation. Hypotension, though unlikely, usually may be controlled with Levarterenol Bitartrate Injection U.S.P. Usefulness of dialysis has not been determined.

Ativan® (IV) for (lorazepam) Anxiety

DOSAGE: Individualize for maximum beneficial effects. Increase dose gradually when needed, giving higher evening dose before increasing daytime doses. Anxiety, usually 2-3mg/day given b.i.d. or t.i.d.; dosage may vary from 1 to 10mg/day in divided doses. For elderly or debilitated, initially 1-2mg/day; insomnia due to anxiety or transient situational stress, 2-4mg h.s.

HOW SUPPLIED: 0.5, 1.0 and 2.0mg tablets.

Wyeth Laboratories
Philadelphia, PA 19101

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CONTINUING MEDICAL EDUCATION

(Continued from Page 322)

May 17-18—**Clinical Concerns in Hemodialysis Therapy.** Rutgers Medical School at Sheraton Harbor Island West Hotel, San Diego. Friday-Saturday. 11.5 hrs. Contact: Richard A. Sherman, MD, Academic Health Science Center, UMDNJ-Rutgers Medical School, CN-19, New Brunswick, NJ 08903.

June 19-21—**Gastroenterology: Recent Developments in Theory and Practice.** UCSF at Mark Hopkins Hotel, San Francisco. Wednesday-Friday. Fees: $375.

June 21-23—**California Society of Internal Medicine—Annual Meeting** at Hotel Del Coronado, Coronado. Friday-Sunday. 3 hrs. Contact: Carol Holland Parlette, CSIM, 703 Market Street, San Francisco 94103.

June 24-28—**Advances in Internal Medicine.** UCSF at Hotel Meridien, San Francisco. Fee: $420.

OBSTETRICS AND GYNECOLOGY

March 16-17—**Uses of Real-time Ultrasound in Gynecology and Infertility.** UCI at Hotel Inter-Continental, San Diego. Saturday-Sunday. 16 hrs.

March 21-24—**Changing Practice of Obstetrical Anesthesiology and High Risk Pregnancy.** UCSF at Hotel Meridien, San Francisco. Thursday-Sunday. 16 hrs.

March 22-24—**Gynecology Surgery with Emphasis on Gynecologic Urology.** UCI at The Palm Springs Marquis, Palm Springs. Friday-Sunday. 15 hrs.

March 27-30—**Horizons in Reproductive Health.** Planned Parenthood and UCSD at Hotel Del Coronado, San Diego. Wednesday-Saturday. 15.5 hrs. Contact: Nomi Feldman, Conference Coord., 3770 Tansy, San Diego 92121. (619) 453-6222.

April 12-14—**Ob/Gyn and Abdominal Sonography: Update '85.** UCSF at Fairmont Hotel, San Francisco. Friday-Sunday. 14.5 hrs.

April 20—**Infertility Update III.** Scripps Clinic and Research Foundation at La Jolla. Saturday. Contact: Scripps Clinic and Research Foundation, 10666 N. Torrey Pines Rd, La Jolla 92037. (619) 455-9100.

OPHTHALMOLOGY

March 21-22—**Reider Laser Symposium in Ophthalmology.** UCI. Thursday-Friday. 13 hrs.

April 12-13—**16th Jules Stein Lecture and Annual Postgraduate Seminar.** JSEI. Saturday-Sunday. 16 hrs. Fee: $375. Contact: Lu Hendricks, Jules Stein Eye Institute, 800 Westwood Plaza, Los Angeles 90024. (213) 825-4617.

May 18—**Neodymium—YAG Laser Course.** Jules Stein Eye Institute at Los Angeles. Saturday. 8 hrs.

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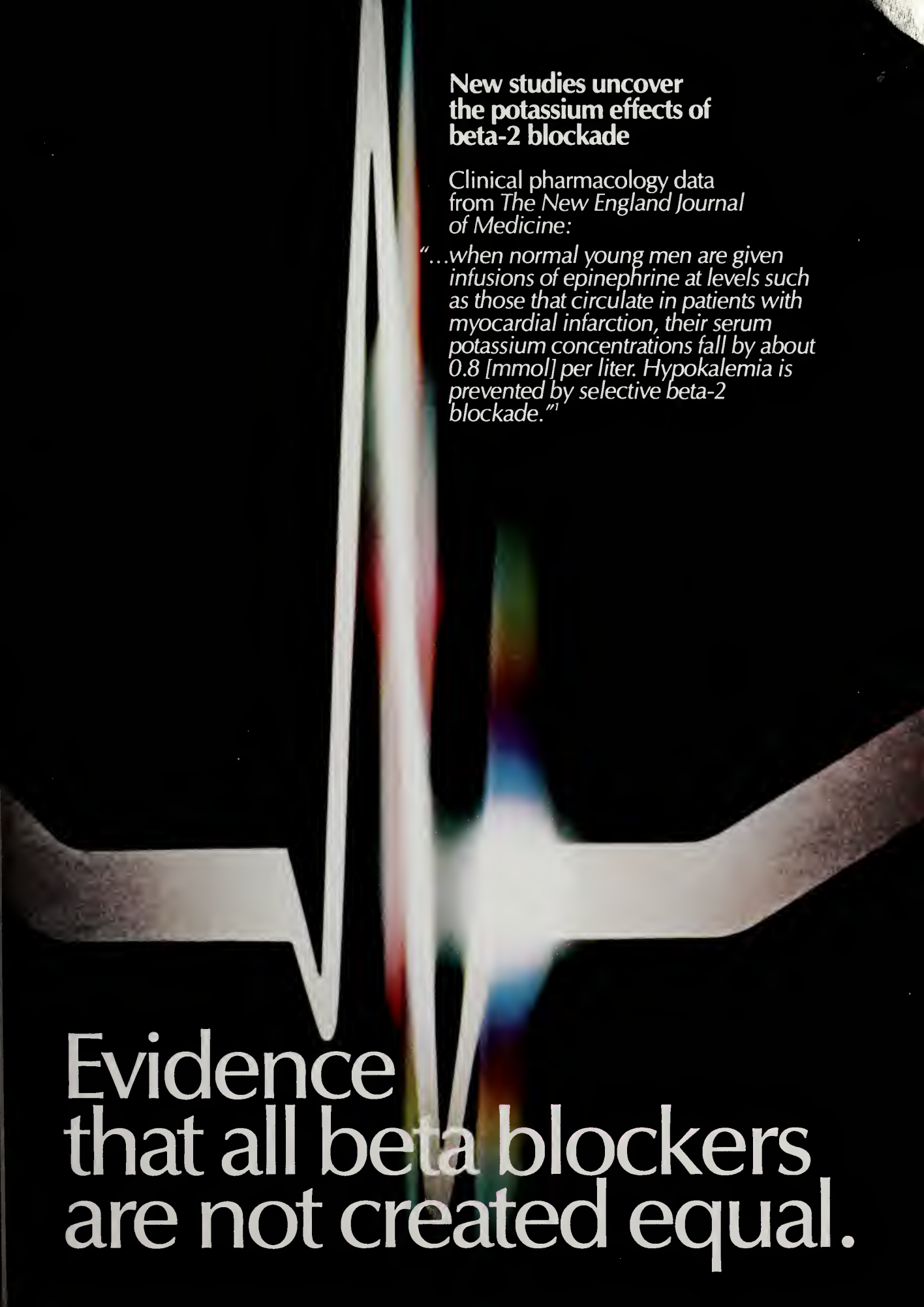


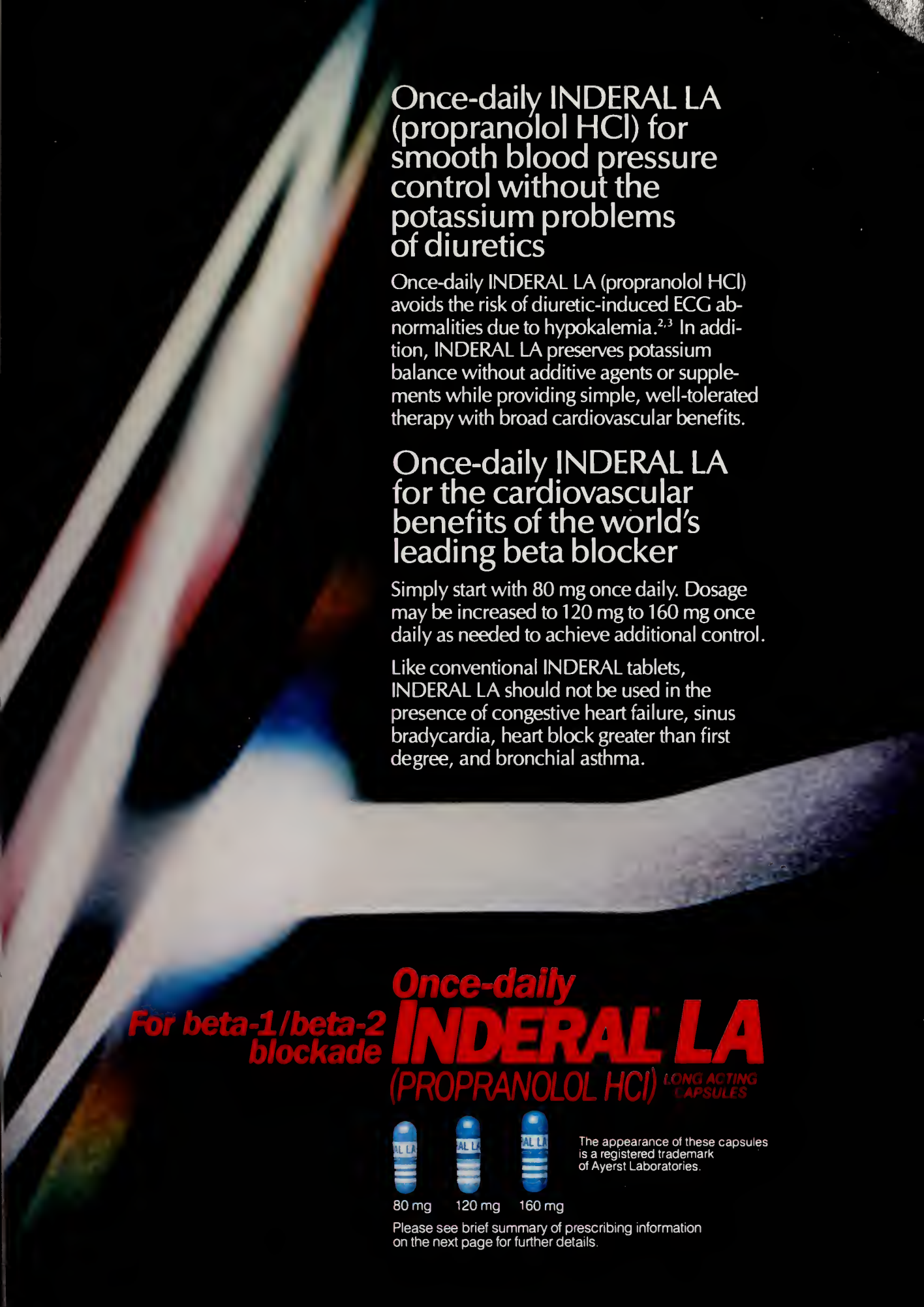
New studies uncover the potassium effects of beta-2 blockade

Clinical pharmacology data from *The New England Journal of Medicine:*

"...when normal young men are given infusions of epinephrine at levels such as those that circulate in patients with myocardial infarction, their serum potassium concentrations fall by about 0.8 [mmol] per liter. Hypokalemia is prevented by selective beta-2 blockade."[1]

Evidence that all beta blockers are not created equal.

Right from the start in hypertension...



Once-daily INDERAL LA (propranolol HCl) for smooth blood pressure control without the potassium problems of diuretics

Once-daily INDERAL LA (propranolol HCl) avoids the risk of diuretic-induced ECG abnormalities due to hypokalemia.[2,3] In addition, INDERAL LA preserves potassium balance without additive agents or supplements while providing simple, well-tolerated therapy with broad cardiovascular benefits.

Once-daily INDERAL LA for the cardiovascular benefits of the world's leading beta blocker

Simply start with 80 mg once daily. Dosage may be increased to 120 mg to 160 mg once daily as needed to achieve additional control.

Like conventional INDERAL tablets, INDERAL LA should not be used in the presence of congestive heart failure, sinus bradycardia, heart block greater than first degree, and bronchial asthma.

For beta-1/beta-2 blockade

Once-daily

INDERAL® LA

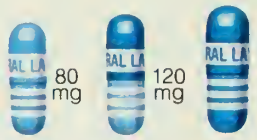
(PROPRANOLOL HCl) LONG ACTING CAPSULES

80 mg 120 mg 160 mg

The appearance of these capsules is a registered trademark of Ayerst Laboratories.

Please see brief summary of prescribing information on the next page for further details.

Once-daily For beta-1/beta-2 blockade INDERAL® LA (PROPRANOLOL HCl) LONG ACTING CAPSULES



The appearance of these capsules is a registered trademark of Ayerst Laboratories

BRIEF SUMMARY *(FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE CIRCULAR.)*

INDERAL® LA brand of propranolol hydrochloride **(Long Acting Capsules)**

DESCRIPTION. Inderal LA is formulated to provide a sustained release of propranolol hydrochloride. Inderal LA is available as 80 mg, 120 mg, and 160 mg capsules.

CLINICAL PHARMACOLOGY. INDERAL is a nonselective beta-adrenergic receptor blocking agent possessing no other autonomic nervous system activity. It specifically competes with beta-adrenergic receptor stimulating agents for available receptor sites. When access to beta-receptor sites is blocked by INDERAL, the chronotropic, inotropic, and vasodilator responses to beta-adrenergic stimulation are decreased proportionately.

INDERAL LA Capsules (80, 120, and 160 mg) release propranolol HCl at a controlled and predictable rate. Peak blood levels following dosing with INDERAL LA occur at about 6 hours and the apparent plasma half-life is about 10 hours. When measured at steady state over a 24-hour period the areas under the propranolol plasma concentration-time curve (AUCs) for the capsules are approximately 60% to 65% of the AUCs for a comparable divided daily dose of INDERAL tablets. The lower AUCs for the capsules are due to greater hepatic metabolism of propranolol, resulting from the slower rate of absorption of propranolol. Over a twenty-four (24) hour period, blood levels are fairly constant for about twelve (12) hours then decline exponentially.

INDERAL LA should not be considered a simple mg for mg substitute for conventional propranolol and the blood levels achieved do not match (are lower than) those of two to four times daily dosing with the same dose. When changing to INDERAL LA from conventional propranolol, a possible need for retitration upwards should be considered especially to maintain effectiveness at the end of the dosing interval. In most clinical settings, however, such as hypertension or angina where there is little correlation between plasma levels and clinical effect, INDERAL LA has been therapeutically equivalent to the same mg dose of conventional INDERAL as assessed by 24-hour effects on blood pressure and on 24-hour exercise responses of heart rate, systolic pressure and rate pressure product. INDERAL LA can provide effective beta blockade for a 24-hour period.

The mechanism of the antihypertensive effect of INDERAL has not been established. Among the factors that may be involved in contributing to the antihypertensive action are (1) decreased cardiac output, (2) inhibition of renin release by the kidneys, and (3) diminution of tonic sympathetic nerve outflow from vasomotor centers in the brain. Although total peripheral resistance may increase initially, it readjusts to or below the pretreatment level with chronic use. Effects on plasma volume appear to be minor and somewhat variable. INDERAL has been shown to cause a small increase in serum potassium concentration when used in the treatment of hypertensive patients.

In angina pectoris, propranolol generally reduces the oxygen requirement of the heart at any given level of effort by blocking the catecholamine-induced increases in the heart rate, systolic blood pressure, and the velocity and extent of myocardial contraction. Propranolol may increase oxygen requirements by increasing left ventricular fiber length, end diastolic pressure and systolic ejection period. The net physiologic effect of beta-adrenergic blockade is usually advantageous and is manifested during exercise by delayed onset of pain and increased work capacity.

In dosages greater than required for beta blockade, INDERAL also exerts a quinidine-like or anesthetic-like membrane action which affects the cardiac action potential. The significance of the membrane action in the treatment of arrhythmias is uncertain.

The mechanism of the antimigraine effect of propranolol has not been established. Beta-adrenergic receptors have been demonstrated in the pial vessels of the brain.

Beta receptor blockade can be useful in conditions in which, because of pathologic or functional changes, sympathetic activity is detrimental to the patient. But there are also situations in which sympathetic stimulation is vital. For example, in patients with severely damaged hearts, adequate ventricular function is maintained by virtue of sympathetic drive which should be preserved. In the presence of AV block, greater than first degree, beta blockade may prevent the necessary facilitating effect of sympathetic activity on conduction. Beta blockade results in bronchial constriction by interfering with adrenergic bronchodilator activity which should be preserved in patients subject to bronchospasm.

Propranolol is not significantly dialyzable.

INDICATIONS AND USAGE. Hypertension: INDERAL LA is indicated in the management of hypertension, it may be used alone or used in combination with other antihypertensive agents, particularly a thiazide diuretic. INDERAL LA is not indicated in the management of hypertensive emergencies.

Angina Pectoris Due to Coronary Atherosclerosis: INDERAL LA is indicated for the long-term management of patients with angina pectoris.

Migraine: INDERAL LA is indicated for the prophylaxis of common migraine headache. The efficacy of propranolol in the treatment of a migraine attack that has started has not been established and propranolol is not indicated for such use.

Hypertrophic Subaortic Stenosis: INDERAL LA is useful in the management of hypertrophic subaortic stenosis, especially for treatment of exertional or other stress-induced angina, palpitations, and syncope. INDERAL LA also improves exercise performance. The effectiveness of propranolol hydrochloride in this disease appears to be due to a reduction of the elevated outflow pressure gradient which is exacerbated by beta-receptor stimulation. Clinical improvement may be temporary.

CONTRAINDICATIONS. INDERAL is contraindicated in 1) cardiogenic shock, 2) sinus bradycardia and greater than first degree block, 3) bronchial asthma, 4) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL.

WARNINGS. CARDIAC FAILURE. Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta blockade may precipitate more severe failure. Although beta blockers should be avoided in overt congestive heart failure, if necessary, they can be used with close follow-up in patients with a history of failure who are well compensated and are receiving digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle.

IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta blockers can, in some cases, lead to cardiac failure. Therefore, at the first sign or symptom of heart failure, the patient should be digitalized and/or treated with diuretics, and the response observed closely; or INDERAL should be discontinued (gradually, if possible).

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following abrupt discontinuance of INDERAL therapy. Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced over at least a few weeks, and the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)— PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

MAJOR SURGERY. The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

INDERAL (propranolol HCl), like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in starting and maintaining the heartbeat has also been reported with beta blockers.

DIABETES AND HYPOGLYCEMIA. Beta-adrenergic blockade may prevent the appearance of certain premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia in labile insulin-dependent diabetes. In these patients, it may be more difficult to adjust the dosage of insulin.

THYROTOXICOSIS. Beta blockade may mask certain clinical signs of hyperthyroidism. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

PRECAUTIONS. *General.* Propranolol should be used with caution in patients with impaired hepatic or renal function. INDERAL (propranolol HCl) is not indicated for the treatment of hypertensive emergencies.

Beta adrenoreceptor blockade can cause reduction of intraocular pressure. Patients should be told that INDERAL may interfere with the glaucoma screening test. Withdrawal may lead to a return of increased intraocular pressure.

Clinical Laboratory Tests. Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

DRUG INTERACTIONS. Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if INDERAL is administered. The added catecholamine-blocking action may produce an excessive reduction of resting sympathetic nervous activity which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility. Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In 18-month studies in both rats and mice, employing doses up to 150 mg/kg/day, there was no evidence of significant drug-induced toxicity. There were no drug-related tumorigenic effects at any of the dosage levels. Reproductive studies in animals did not show any impairment of fertility that was attributable to the drug.

Pregnancy. Pregnancy Category C. INDERAL has been shown to be embryotoxic in animal studies at doses about 10 times greater than the maximum recommended human dose.

There are no adequate and well-controlled studies in pregnant women. INDERAL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. INDERAL is excreted in human milk. Caution should be exercised when INDERAL is administered to a nursing woman.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS. Most adverse effects have been mild and transient and have rarely required the withdrawal of therapy.

Cardiovascular. bradycardia, congestive heart failure, intensification of AV block, hypotension, paresthesia of hands, thrombocytopenic purpura, arterial insufficiency, usually of the Raynaud type.

Central Nervous System. lightheadedness, mental depression manifested by insomnia, lassitude, weakness, fatigue, reversible mental depression progressing to catatonia, visual disturbances, hallucinations, an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Gastrointestinal. nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis.

Allergic. pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Respiratory. bronchospasm.

Hematologic. agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Auto-Immune. In extremely rare instances, systemic lupus erythematosus has been reported.

Miscellaneous. alopecia, LE-like reactions, psoriasiform rashes, dry eyes, male impotence, and Peyronie's disease have been reported rarely. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been associated with propranolol.

DOSAGE AND ADMINISTRATION. INDERAL LA provides propranolol hydrochloride in a sustained-release capsule for administration once daily. If patients are switched from INDERAL tablets to INDERAL LA capsules, care should be taken to assure that the desired therapeutic effect is maintained. INDERAL LA should not be considered a simple mg for mg substitute for INDERAL. INDERAL LA has different kinetics and produces lower blood levels. Retitration may be necessary especially to maintain effectiveness at the end of the 24-hour dosing interval.

HYPERTENSION—*Dosage must be individualized.* The usual initial dosage is 80 mg INDERAL LA once daily, whether used alone or added to a diuretic. The dosage may be increased to 120 mg once daily or higher until adequate blood pressure control is achieved. The usual maintenance dosage is 120 to 160 mg once daily. In some instances a dosage of 640 mg may be required. The time needed for full hypertensive response to a given dosage is variable and may range from a few days to several weeks.

ANGINA PECTORIS—*Dosage must be individualized.* Starting with 80 mg INDERAL LA once daily, dosage should be gradually increased at three to seven day intervals until optimum response is obtained. Although individual patients may respond at any dosage level, the average optimum dosage appears to be 160 mg once daily. In angina pectoris, the value and safety of dosage exceeding 320 mg per day have not been established.

If treatment is to be discontinued, reduce dosage gradually over a period of a few weeks (see WARNINGS).

MIGRAINE—*Dosage must be individualized.* The initial oral dose is 80 mg INDERAL LA once daily. The usual effective dose range is 160-240 mg once daily. The dosage may be increased gradually to achieve optimum migraine prophylaxis. If a satisfactory response is not obtained within four to six weeks after reaching the maximum dose, INDERAL LA therapy should be discontinued. It may be advisable to withdraw the drug gradually over a period of several weeks.

HYPERTROPHIC SUBAORTIC STENOSIS—80-160 mg INDERAL LA once daily.

PEDIATRIC DOSAGE—At this time the data on the use of the drug in this age group are too limited to permit adequate directions for use.

REFERENCES

1. Epstein FH, Rosa RM. Adrenergic control of serum potassium. *N Engl J Med* 1983; 309:1450-1451. **2.** Holland OB, Nixon JV, Kuhnert L. Diuretic-induced ventricular ectopic activity. *Am J Med* 1981;70:762-768. **3.** Holme I, Helgeland A, Hjermann I, et al: Treatment of mild hypertension with diuretics. The importance of ECG abnormalities in the Oslo study and in MRFIT. *JAMA* 1984;251:1298-1299.

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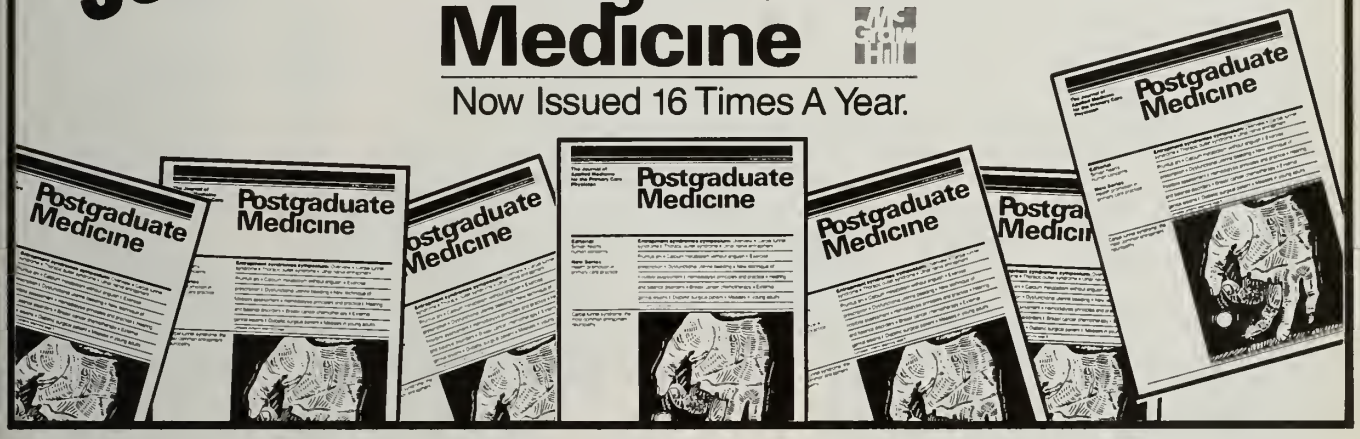


CONTINUING MEDICAL EDUCATION

(Continued from Page 324)

Fee: $200. Contact: Lu Hendricks, JSEI, 800 Westwood Plaza, Los Angeles 90024. (213) 825-4617.

June 6-8—**Cosmetic Blepharoplasty Workshop.** Jules Stein Eye Institute at Los Angeles. Thursday-Saturday. 18 hrs. Fee: $750. Contact: Lu Hendricks, JSEI, 800 Westwood Plaza, Los Angeles 90024. (213) 825-4617.

PATHOLOGY

May 23-24—**Symposium on Current Issues in Anatomic Pathology.** UCSF. Thursday-Friday.

PEDIATRICS

April 10—**Pediatrics: Infections in Infants and Children.** LLU. Wednesday. 4 hrs.

April 17-19—**10th Annual Symposium "Care of the Sick Newborn."** UCI at Hyatt Regency Hotel, Long Beach. Wednesday-Friday. 17 hrs.

April 19-20—**Annual Pediatric Program.** UCD at Sacramento Inn, Sacramento. Friday-Sunday.

April 19-21—**3rd Annual Avoiding the Pitfalls of Pediatric Office Orthopedics.** UCLA at Americana Canyon Hotel, Palm Springs. Friday-Sunday. 10.5 hrs. Fee: $240.

May 13-17—**The 15th Annual Review of Pediatrics.** USC at Los Angeles. Monday-Friday. 26 hrs. Fee: $360.

May 15—**Los Angeles Pediatric Society—Annual Spring Meeting** at Los Angeles. Wednesday. Contact: Eve Black, Exec. Sec., PO Box 2022, Inglewood 90305. (213) 757-1198.

May 30-June 1—**Pediatric Rehabilitation Program.** UCD at Doubletree Inn, Monterey. Thursday-Saturday.

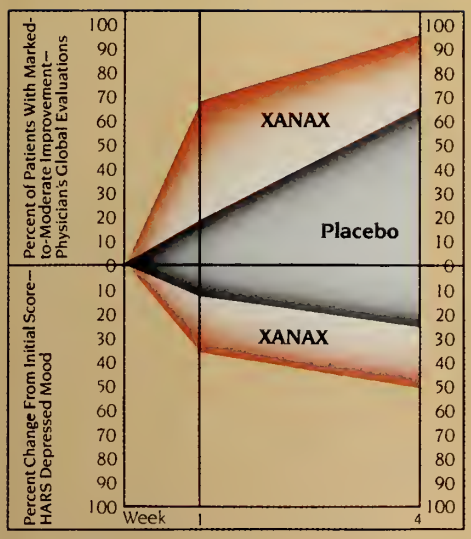
June 21-22—**Pediatric Pulmonary Update—1985.** Children's Hospital and Health Center at San Diego Hilton Beach and Tennis Resort. Friday-Saturday. Contact: Sung Min Park, MD, Children's Hospital and Health Center, 8001 Frost Street, San Diego 92123. (619) 576-5854.

June 22-29—**3rd National Kaiser Permanente Pediatrics Conference** at Maui, Hawaii. One Week. 22.5 hrs. Fee: $100. Contact: Steven Black, MD (415) 428-5815.

(Continued on Page 332)

In 7 of 10
anxious
geriatrics...
Anxiety and
depressive
symptoms
go hand
in hand.

Xanax rapidly relieves anxiety with depressive symptoms.



In a recent clinical study[1] of 83 geriatric patients with clinical anxiety, 73% were diagnosed as having symptoms of depressed mood.

XANAX is well suited for therapy because it demonstrates greater efficacy than placebo in reducing the Hamilton Anxiety Rating Scale Total Score and individual items including depressed mood (see Figure).

With clinical advantages for geriatric patients.

- **Rapidly relieves** the symptoms of anxiety
- **Rapidly relieves** associated depressed mood
- **Well tolerated**—mild, transient drowsiness, the most commonly reported side effect the first week of therapy, shows a marked decrease thereafter and is not significantly different from that of placebo
- **Does not cause** cardiotoxicity
- **Specific geriatric dosage**—0.25 mg, two or three times daily

1. Cohn JB. Double-blind safety and efficacy comparison of alprazolam and placebo in the treatment of anxiety in geriatric patients. *Curr Ther Res* 1984;35(1):100-112

Xanax® 0.25 mg Tablets
alprazolam C-IV

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Kalamazoo, Michigan 49001 USA

Please see next page for brief summary of prescribing information.

XANAX® Tablets
(alprazolam) C

CONTRAINDICATIONS
Patients with sensitivity to this drug or other benzodiazepines and in acute narrow angle glaucoma

WARNINGS
Not of value in psychotic patients. Caution patients against hazardous occupations requiring complete mental alertness and about the simultaneous ingestion of alcohol and other CNS depressant drugs.

Benzodiazepines can cause fetal harm in pregnant women. Warn patients of the potential hazard to the fetus. Avoid during the first trimester.

PRECAUTIONS
General: The dosage of XANAX Tablets should be reduced or withdrawn gradually, since withdrawal seizures have been reported upon abrupt withdrawal. If XANAX is combined with other psychotropics or anticonvulsant drugs, consider drug potentiation. (See Drug Interaction section.) Exercise the usual precautions regarding size of the prescription for depressed or suicidal patients. In elderly and debilitated patients, use the lowest possible dosage. (See Dosage and Administration.) Observe the usual precautions in treating patients with impaired renal or hepatic function.

Information for Patients: Alert patients about (a) consumption of alcohol and drugs, (b) possible fetal abnormalities, (c) operating machinery or driving, (d) not increasing dose of the drug due to risk of dependence, (e) not stopping the drug abruptly. *Laboratory Tests:* Not ordinarily required in otherwise healthy patients. *Drug Interactions:* Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistamines, ethanol and other CNS depressants. Pharmacokinetic interactions with benzodiazepines have been reported. *Drug/Laboratory Test Interactions:* No consistent pattern for a specific drug or specific test. *Carcinogenesis, Mutagenesis, Impairment of Fertility:* No carcinogenic potential or impairment of fertility in rats. *Pregnancy:* See Warnings. *Nonteratogenic Effects:* The child born of a mother on benzodiazepines may be at some risk for withdrawal symptoms and neonatal flaccidity. *Labor and Delivery:* No established use. *Nursing Mothers:* Benzodiazepines are excreted in human milk. Women on XANAX should not nurse. *Pediatric Use:* Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS
Side effects are generally observed at the beginning of therapy and usually disappear with continued medication. In the usual patient, the most frequent side effects are likely to be an extension of the pharmacological activity of XANAX, e.g., drowsiness or lightheadedness.

Central nervous system: Drowsiness, lightheadedness, depression, headache, confusion, insomnia, nervousness, syncope, dizziness, akathisia, and tiredness/sleepiness.

Gastrointestinal: Dry mouth, constipation, diarrhea, nausea/vomiting, and increased salivation.

Cardiovascular: Tachycardia/palpitations, and hypotension.

Sensory: Blurred vision.

Musculoskeletal: Rigidity and tremor.

Cutaneous: Dermatitis/allergy.

Other side effects: Nasal congestion, weight gain, and weight loss.

In addition, the following adverse events have been reported with the use of anxiolytic benzodiazepines: dystonia, irritability, concentration difficulties, anorexia, loss of coordination, fatigue, sedation, slurred speech, jaundice, musculoskeletal weakness, pruritus, diplopia, dysarthria, changes in libido, menstrual irregularities, incontinence and urinary retention.

Paradoxical reactions such as stimulation, agitation, increased muscle spasticity, sleep disturbances, and hallucinations may occur. Should these occur, discontinue the drug.

During prolonged treatment, periodic blood counts, urinalysis, and blood chemistry analysis are advisable. Minor EEG changes, of unknown significance, have been observed.

DRUG ABUSE AND DEPENDENCE
Physical and Psychological Dependence: Withdrawal symptoms have occurred following abrupt discontinuance of benzodiazepines. Withdrawal seizures have occurred upon rapid decrease or abrupt discontinuation of therapy. In all patients, dosage should be gradually tapered under close supervision. Patients with a history of seizures or epilepsy should not be abruptly withdrawn from XANAX. Addiction-prone individuals should be under careful surveillance. *Controlled Substance Class:* XANAX is a controlled substance and has been assigned to schedule IV.

DOSAGE AND ADMINISTRATION
The usual starting dose is 0.25 to 0.5 mg, t.i.d. Maximum total daily dose is 4 mg. In the elderly or debilitated, the usual starting dose is 0.25 mg, two or three times daily. Reduce dosage gradually when terminating therapy, by no more than one milligram every three days.

CAUTION: FEDERAL LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION.

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(Continued from Page 329)

PSYCHIATRY

March 29-31—**General Psychiatry Board Review.** UCSF at Golden Gateway Holiday Inn, San Francisco. Friday-Sunday.

April 27-28—**The Cutting Edge 1985—Clinical Applications of Kohut's Theories on Narcissism.** UCSD. Saturday-Sunday. 12.5 hrs.

RADIOLOGY

March 18-23—**Diagnostic Imaging 1985.** UCSF at Waiohai Hotel, Kauai. Monday-Saturday. 26 hrs. Fee: $425.

April 14-19—**Adult and Pediatric Radiology for Emergency Physicians.** UCSD at Waiohai Hotel, Kauai. Sunday-Friday. 21 hrs. Fee: $315-430.

April 29-May 3—**5th Annual Residents Radiology Review Course.** UCSD at Town and Country Inn, San Diego. Monday-Friday.

May 17-19—**10th Annual Spring Diagnostic Ultrasound Conference.** Los Angeles Radiological Society at Century Plaza Hotel, Los Angeles. Friday-Sunday. 17 hrs. Contact: Zbigniew Petrovich, MD, c/o L.A. Radiological Society, PO Box 91215, Los Angeles 90009-1215. (213) 642-0921.

May 19-25—**5th Annual Post Conference Seminar.** Los Angeles Radiological Society at Turtle Bay Hilton and Country Club, Kahuku, Oahu. Sunday-Saturday. 18 hrs. Contact: Zbigneiw Petrovich, MD, c/o Los Angeles Radiological Society, PO Box 91215, Los Angeles 90009-1215. (213) 642-0921.

SPORTS MEDICINE

March 18-22—**University of Hawaii Sports Medicine Course.** Ohio State University at Princess Kaiulani Hotel, Waikiki, HI. Monday-Friday. 18 hrs. Fee: $280. Contact: Ms. Joy Lewis, Box CEW-CCECS, 2530 Dole St., Honolulu, HI 96822. (808) 948-8244.

SURGERY

March 17-20—**22nd Annual UCLA Seminar on Controversial Areas in Surgery.** UCLA at Hilton Rivera Hotel, Palm Springs. Sunday-Wednesday. 14 hrs.

June 17-21—**Basic Microsurgery Training Workshop.** UCSD at San Diego. Monday-Friday. 34 hrs. Fee: $1,200.

March 18-22—**Basic Microsurgery Training Workshop.** UCSD. Monday-Friday. 34 hrs. Fee: $1,200. Contact: UCSD.

March 22-24—**2nd Annual Symposium on Prosthetic Ligament Reconstruction of the Knee.** UCLA at Sheraton Plaza Hotel, Palm Springs. Friday-Sunday.

(Continued on Page 422)

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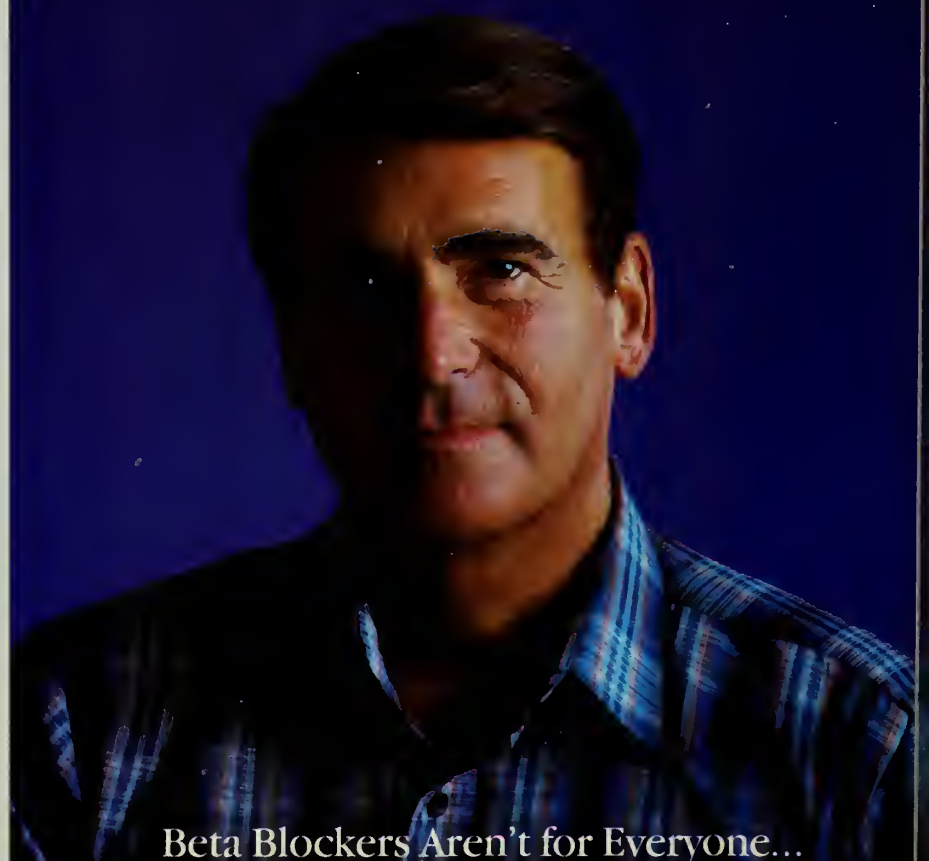
In Hypertensives Over 50, Diuretics Are Preferred

The 1984 Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure recommends diuretics as the favored monotherapy in patients over 50 years of age, regardless of sex or race.



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For Hypertensive Patients*Over 50

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Used with Confidence for over 19 Years

Serum K^+ and BUN should be checked periodically (see Warnings and Precautions).

Before prescribing, see complete prescribing information in SK&F CO. literature or *PDR*. The following is a brief summary.

* **WARNING**

This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Contraindications: Concomitant use with other potassium-sparing agents such as spironolactone or amiloride. Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics.

Precautions: The bioavailability of the hydrochlorothiazide component of 'Dyazide' is about 50% of the bioavailability of the single entity. Theoretically, a patient transferred from the single entities of Dyrenium (triamterene, SK&F CO.) and hydrochlorothiazide may show an increase in blood pressure or fluid retention. Similarly, it is also possible that the lesser hydrochlorothiazide bioavailability could lead to increased serum potassium levels. However, extensive clinical experience with 'Dyazide' suggests that these conditions have not been commonly observed in clinical practice. Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids, and during concurrent use with amphotericin B or corticosteroids or corticotropin [ACTH]). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Cumulative effects of the drug may develop in patients with impaired renal function. Thiazides should be used with caution in patients with impaired hepatic function. They can precipitate coma in patients with severe liver disease. Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic and hemolytic anemia have been reported with thiazides. Thiazides may cause manifestation of latent diabetes mellitus. The effects of oral anticoagulants may be decreased when used concurrently with hydrochlorothiazide; dosage adjustments may be necessary. Clinically insignificant reductions in arterial responsiveness to norepinephrine have been reported. Thiazides have also been shown to increase the paralyzing effect of nondepolarizing muscle relaxants such as tubocurarine. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. Triamterene has been found in renal stones in association with the other usual calculus components. Therefore, 'Dyazide' should be used with caution in patients with histories of stone formation. A few occurrences of acute renal failure have been reported in patients on 'Dyazide' when treated with indomethacin. Therefore, caution is advised in administering nonsteroidal anti-inflammatory agents with 'Dyazide'. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine. Hypokalemia is uncommon with 'Dyazide', but should it develop, corrective measures should be taken such as potassium supplementation or increased dietary intake of potassium-rich foods. Corrective measures should be instituted cautiously and serum potassium levels determined. Discontinue corrective measures and 'Dyazide' should laboratory values reveal elevated serum potassium. Chloride deficit may occur as well as dilutional hyponatremia. Concurrent use with chlorpropamide may increase the risk of severe hyponatremia. Serum PBI levels may decrease without signs of thyrcid disturbance. Calcium excretion is decreased by thiazides. 'Dyazide' should be withdrawn before conducting tests for parathyroid function.

Thiazides may add to or potentiate the action of other antihypertensive drugs.

Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity.

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Standardized Treatment of Severe Methanol Poisoning With Ethanol and Hemodialysis

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Seven patients with methanol poisoning were treated with ethanol, hemodialysis and supportive measures. The interval between ingestion and initiation of ethanol therapy varied from 3 to 67 hours and from ingestion to dialysis from 9 to 93 hours. All patients survived, but one had permanent visual impairment. A 10% ethanol solution administered intravenously is a safe and effective antidote for severe methanol poisoning. Ethanol therapy is recommended when plasma methanol concentrations are higher than 20 mg per dl, when ingested doses are greater than 30 ml and when there is evidence of acidosis or visual abnormalities in cases of suspected methanol poisoning.

(Ekins BR, Rollins DE, Duffy DP, et al: Standardized treatment of severe methanol poisoning with ethanol and hemodialysis. West J Med 1985 Mar; 142:337-340)

The ingestion of large amounts of methanol is accompanied by metabolic acidosis, respiratory depression and optic nerve degeneration as a result of its metabolism to formaldehyde and subsequently to formic acid.[1,2] Ethanol has a greater affinity than methanol for the enzyme alcohol dehydrogenase, which is responsible for the initial step in methanol metabolism.[3] A suggested method of treating methanol poisoning is the administration of ethanol, thus reducing the formation of the toxic metabolites of methanol. Excess methanol is then removed from the body by hemodialysis.[4]

Guidelines for administering ethanol are inconsistent and range from the oral administration of commercially available whiskey to the intravenous administration of large volumes of 5% ethanol. The specific gravity of ethanol solutions varies with their concentration, thus making calculation of the volume of ethanol to be administered difficult.[5]

The present study was undertaken to determine the feasibility of treating cases of acute methanol poisoning with a commercially available 10% (vol per vol) ethanol solution administered intravenously according to a protocol based on the known pharmacokinetics of ethanol. The protocol is simple, reliable and provides a rational approach for the use of ethanol as an antidote.

Methods

Plasma ethanol and methanol concentrations were analyzed by gas liquid chromatography using a hydrogen flame detector and a 5% Carbowax on a 60/80 column with *N*-propanol as the internal standard. The sensitivity of the assay for both methanol and ethanol is 5 mg per dl. Linearity for methanol ranged from 5 to 300 mg per dl and for ethanol from 5 to 350 mg per dl.

Patients were initially treated with gastric lavage, activated charcoal, saline cathartic and fluids given intravenously—including sodium bicarbonate solution when appropriate—and then transferred to the University of Utah Medical Center. The criterion for beginning ethanol therapy was a history of ingesting more than 30 ml of methanol or a plasma methanol concentration greater than 20 mg per dl. Plasma methanol concentrations of less than 20 mg per dl have historically not been associated with signs of serious intoxication. In a prospective study of 46 cases based on clinical outcomes, it was concluded that a concentration of methanol in the range of 20 to 30 mg per dl would be a safe level at which ethanol therapy could be stopped.[6] The criterion for simultaneous ethanol therapy and hemodialysis was a plasma methanol concentration greater than 50 mg per dl or

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metabolic acidosis unresponsive to sodium bicarbonate given intravenously.[4] The clinical information from seven consecutive patients with severe methanol poisoning is presented in Table 1.

A commercially available 10% (vol per vol) ethanol solution in 5% dextrose in water (McGaw Laboratories, Chicago) was administered to each patient. Calculation of the loading dose (LD) of ethanol was based on a desired plasma concentration (C_p) of 100 mg per dl[7] and a volume distribution (V_d) of 600 ml per kg of body weight[8] using the formula:

$$LD = C_p \times V_d$$
$$= 600 \text{ mg/kg}$$

The intravenous infusion rate (K_o) to maintain an ethanol plasma concentration at 100 mg per dl was based on the following equation:

$$K_o = \frac{(V_{max}) \quad (C_p)}{(K_m + C_p)}$$

where V_{max} is the maximum ethanol elimination rate and K_m is the Michaelis-Menten constant for ethanol. A V_{max} of 124 mg per kg per hour (range, 75 mg per kg per hour for nondrinkers and 175 mg per kg per hour for long-term drinkers) and a K_m of 13.8 mg per dl were used to calculate the maintenance infusion.[9,10] Using these figures a maintenance infusion rate of 109 mg per kg per hour was obtained. The loading and maintenance doses are given together over the first hour (600 mg per kg plus 109 mg per kg). The maintenance ethanol infusion rate during dialysis was calculated using pharmacokinetic values measured in patient 2. The clearance of ethanol during dialysis (Cl_D) was determined from this patient's plasma ethanol half-life (T½) of 2.75 hours, using the following equation:

$$Cl_D = 0.693 \times V_d / T½$$

The ethanol clearance during dialysis was calculated as 151 mg per kg per hour. The ethanol infusion rate during dialysis (K_{o_D}) was calculated from K_o, Cl_D and C_p by the following equation:

$$K_{o_D} = K_o + (Cl_D \times C_p)$$
$$= 109 \text{ mg/kg/hour} + (151 \text{ ml/kg/hour} \times 100 \text{ mg/dl})$$
$$= 260 \text{ mg/kg/hour}$$

Hemodialysis was carried out with a Travenol RSP delivery system in a standard recirculating-single pass configuration for patient 1 and in a single pass configuration with a dialysate flow of 400 ml per minute for the other six patients.* Large surface area plate or hollow fiber dialyzers were used for each patient. The Seldinger technique of femoral vein catherization was used for double catheter access with high flows and minimal recirculation. Methanol clearance during dialysis was calculated using standard equations.[11]

Results

The clinical data from seven consecutive patients with methanol poisoning are given in Table 1. The amount of methanol ingested and the time from ingestion until an initial plasma methanol concentration was obtained varied considerably in our patients. Patient 6 allegedly consumed methanol over a 24-hour period, precluding calculation of the exact time since ingestion. All patients survived and, except for patient 2, had normal vision with no signs of optic neuritis at time of discharge. Patient 2 suffered severe ocular damage characterized by blurring of all images and central scotomata

*Gregory H. Done, CHT, provided technical assistance and gathered data.

TABLE 1.—*Summary of Findings in Seven Men With Methanol Poisoning Treated With Ethanol Therapy and Dialysis**

Patient	Age, Years	Estimated Amount of Methanol Ingested	Time From Ingestion to First Methanol Level	Initial Serum Methanol	Time From Ingestion to Giving Ethanol	Duration of Ethanol Therapy	Range of Ethanol Serum Levels	Initial Arterial Blood Gases			Anion Gap†	Time From Ingestion to Dialysis	Predialysis Methanol Concentration	Postdialysis Methanol Concentration	Clearance of Methanol	Duration of Dialysis	Outcome
								pH	P_{CO_2}	HCO_3							
		ml	hours	mg/dl	hours	hours	mg/dl		mm of mercury	mEq/liter	mEq/liter	hours	mg/dl	mg/dl	ml/min	hours	
1‡	48	373	2	373	4.0	87	55-197	7.41	10.0	6.1	30.9	9	340	45	151	7/5.5	Survived; normal vision
2	39	373	9	220	3.0	24	55-145	7.10	18.0	7.0	31	13	220	14	255	9	Survived; bilateral ocular damage
3	16	unknown	48	49	49.0	16	58-162	7.22	20.0	8.0	26	56	49	10	253	7.5	Survived; normal vision
4§	20	180	4	377	5.5	33	75-194	7.39	37.0	22.0	10	15	340	20	228	11	Survived; normal vision
5	20	300	14	158	15.0	12	70-103	7.35	17.0	9.2	14	17	65	20	286	6	Survived; normal vision
6	20	unknown	67	52	67.0	65	75-208	7.33	25.0	9.0	15	93	42	5	225	4	Survived; normal vision
7	20	240	48	46	48.0	12	80-160	7.16	26.1	7.3	26	56	43	10	260	4	Survived; normal vision

P_{CO_2} = carbon dioxide pressure; HCO_3 = bicarbonate anion

*Access to the circulation was by double needle except for patient 3 in whom a single needle was used. A Terumo 1.5m² dialyzer was used for each patient except patient 3 in whom a PPD 1.3m² dialyzer was used. The mean blood flow in all cases ranged from 225 to 350 ml/min.

†Anion gap calculated as follows: serum sodium level − (bicarbonate + chloride).

‡Patient was given 40% ethanol intravenously for 10 hours, which was changed to 10% ethanol in a solution of 5% dextrose in water. The patient underwent dialysis twice, the second 21 hours after the first.

§Patient was given ethanol intravenously and orally as a loading dose. Exact oral dose retained was unclear because of vomiting. He was then maintained on 10% ethanol given intravenously.

with small islands of normal vision around the macula. This patient came into treatment with a prominent acidosis that may have played a larger role in the toxicity. An error in the time element of the ingestion and the initiation of treatment may have also contributed to greater toxicity.

In five of seven patients ethanol therapy was started by the referring physician, with clinical information being supplied by telephone consultation. The loading and maintenance doses of ethanol provided therapeutic plasma concentrations of ethanol. The mean plasma ethanol concentration obtained between one and two hours of beginning the ethanol therapy was 118 ± 43 mg per dl (mean ± standard deviation [SD]) for the seven patients. Infusion in forearm veins was mildly uncomfortable for some patients; postinfusion phlebitis was not observed, however.

Hemodialysis was continued until the plasma methanol concentration was less than 20 mg per dl (except in patient 1). The mean whole blood clearance of methanol was 251 ± 22 ml per minute (mean ± SD) in the six patients in whom a single pass dialysis was used. This was considerably higher than previously reported for a recirculating-single pass system.[12]

Figure 1 shows the entire course of therapy for patient 2. It is evident that the ethanol therapy delayed the metabolism of methanol in that the methanol concentration did not decrease until hemodialysis was initiated. Hemodialysis resulted in a prompt reduction in the plasma methanol concentration, resolution of acidosis and improvement in the patient's clinical condition. When we used the described ethanol protocol during dialysis, the plasma ethanol concentration never fell below a concentration that would inhibit alcohol dehydrogenase.

Discussion

The initial plasma concentration in cases of acute methanol poisoning usually reflects the amount ingested and the time between ingestion and blood collection. In patient 4 the plasma methanol concentration, measured four hours after ingestion, was 377 mg per dl, yet the patient had only mild metabolic acidosis. On the other hand, in patient 7 the initial plasma methanol concentration, measured 48 hours after ingestion, was 46 mg per dl, and the patient had severe acidosis with a wide anion gap. This discrepancy between plasma concentration of methanol and clinical signs of toxicity is compatible with the concept that methanol needs to be metabolized to formaldehyde and formic acid before the toxicity is fully manifest.[3] This provides the rationale for ethanol therapy, which inhibits the metabolism of methanol. The enzyme alcohol dehydrogenase, responsible for the generation of formaldehyde from methanol, has a higher affinity for ethanol than for methanol. Thus, ethanol is preferentially metabolized and methanol can be eliminated by nonmetabolic routes, including hemodialysis.

The data of this study, obtained in a prospective manner from seven consecutive patients, indicate that commercially available 10% (vol per vol) ethanol solution can be safely and easily administered intravenously to treat cases of acute methanol poisoning. The doses of 10% ethanol to be administered as a loading dose, maintenance dose and a maintenance dose during hemodialysis are shown in Table 2. It should be noted that during the first hour of ethanol therapy the loading dose (600 mg per kg) and the maintenance dose (109 mg per kg) must be given. This is to compensate for the metabolism of the loading dose that occurs during the initial hour of therapy. When these doses are used, the plasma ethanol concentration one to two hours later is predictably in the 100 mg per dl range. Plasma ethanol levels should be monitored hourly for the first several hours and continued until good control is obtained. Once the desired plasma level is obtained, sampling can decrease to every two to four hours. Maintenance ethanol infusion rates may differ from those in Table 2 due to variations in the rate of ethanol metabolism. When the recom-

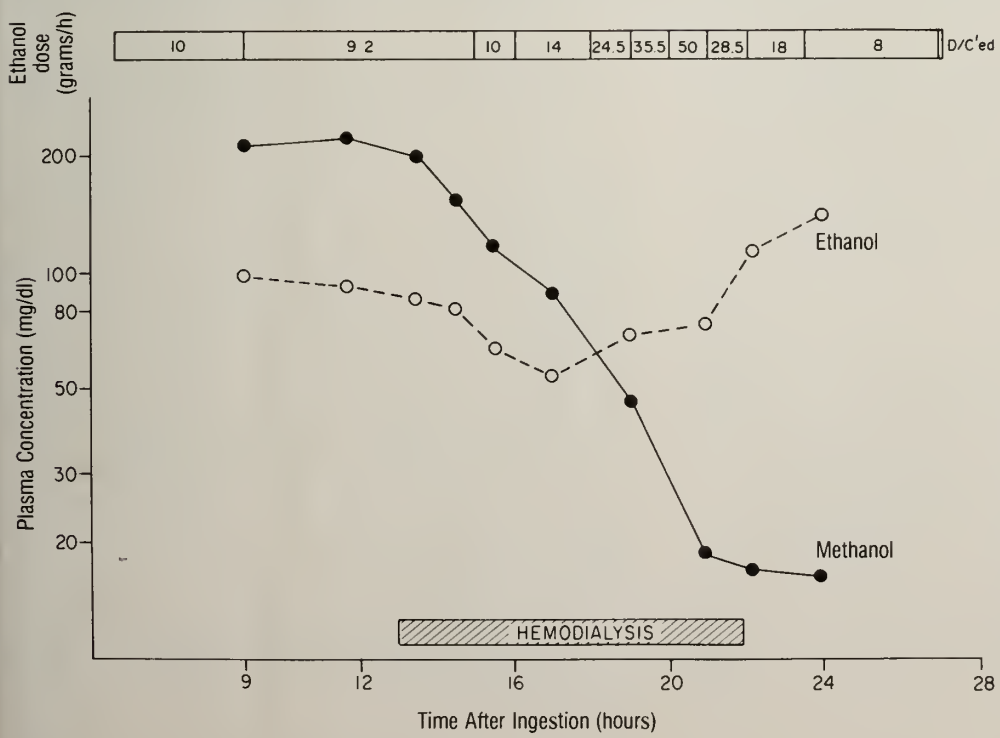

Figure 1.—Ethanol and methanol plasma concentrations from patient 2, plotted as a function of time. The ethanol dose is represented as a composite amount given during the blocks of time represented. It should be noted that the dose of ethanol was not increased until five hours after starting dialysis, resulting in a decrease in plasma ethanol.
D/C'ed = discontinued

TABLE 2.—*Protocol for Ethanol Therapy in Cases of Methanol Overdose*

Type of Dose	*Dose*	*Rate of Infusion of 10% Ethanol*
First hour, ml/kg body weight*	709	8.86
Maintenance dose, ml/kg/h	109	1.36
Maintenance dose during dialysis, ml/kg/h†	260	3.25

*First hour dose includes loading dose and first-hour maintenance dose.

†Maintenance dose during dialysis may have to be adjusted according to efficiency of the dialyzer.

mended doses of 10% ethanol are administered during dialysis, relatively stable plasma ethanol concentrations are maintained. Maintenance of adequate ethanol concentrations during dialysis is essential but is complicated by the increased clearance of ethanol during the procedure. Variations in blood flow rate and dialyzer efficiency will dramatically influence the amount of ethanol removed during dialysis. During dialysis sampling should be done at least hourly. The figures for maintenance ethanol infusion in Table 2 may have to be adjusted according to variations in these factors. It is practical to measure the plasma ethanol concentrations during dialysis and to make the appropriate adjustments in the infusion rate.

The oral route of administration of ethanol has been advocated in cases of acute methanol poisoning.[5] There are several circumstances that limit the use of oral ethanol as an antidote in methanol poisonings. These include erratic absorption of ethanol, severe nausea and vomiting, the concurrent use of activated charcoal and delay in initiating treatment while the stomach is being emptied. In the seven patients reported here, there were no complications as a result of the intravenous administration of ethanol in a 10% solution. There was minimal discomfort associated with the procedure and neither thrombosis nor phlebitis developed, a finding consistent with other investigations.[13] The same protocol should be applicable to ethylene glycol poisoning.[5]

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Clinical Symptoms in Patients With Sustained Ventricular Tachycardia

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We questioned 113 patients with subsequently diagnosed sustained ventricular tachycardia (VT) regarding the symptoms that prompted their seeking hospital treatment, eliciting the following: 15% of patients had lost consciousness, 15% had near syncope, 35% had mild lightheadedness and 35% had no cerebral symptoms. Patients with preexisting congestive heart failure or a VT rate of 200 beats per minute or greater more often lost consciousness. Other symptoms included palpitations in 57% of patients, chest pain in 27%, dyspnea in 25%, weakness in 6%, nausea or diaphoresis in 3% each and flushing in 2%. In approximately 50% of patients who had mild lightheadedness or no cerebral symptoms, their condition was incorrectly diagnosed as supraventricular tachycardia based on the absence of severe symptoms during the tachycardia. In some patients, VT may be associated with mild or atypical symptoms. The differentiation of supraventricular from ventricular tachycardia should be based on electrocardiographic criteria and should not be influenced by the nature or severity of a patient's symptoms. The severity of cerebral symptoms is at least partially related to the VT rate and a patient's underlying heart disease.

(Morady F, Shen EN, Bhandari A, et al: Clinical symptoms in patients with sustained ventricular tachycardia. West J Med 1985 Mar; 142:341-344)

Ventricular tachycardia (VT) is a potentially fatal arrhythmia and is the second most common cause, after ventricular fibrillation, of out-of-hospital cardiac arrest.[1-5] Ventricular tachycardia has typically been described as a serious arrhythmia that is nearly always associated with severe symptoms such as loss of consciousness or seizures and nearly always requires emergent treatment, especially when it occurs in patients who have structural heart disease and when the VT rate is rapid (200 beats per minute or more).[6-11] Perhaps less well appreciated is that VT need not result in severe hypotension or shock. Although there have been several reports of patients who had mild symptoms associated with VT, these reports have been based on small numbers of patients, many of whom were young and had no apparent structural heart disease.[12-20]

In our experience, a significant proportion of patients presenting with sustained VT may not have severe symptoms requiring emergent treatment, even when the VT rate is rapid and the patient has structural heart disease. We have frequently noted cases in which VT was incorrectly diagnosed as supraventricular tachycardia because of a patient's mild symptoms. We describe herein the clinical symptoms in a large group of patients who sought hospital treatment for what proved to be sustained VT. Our observations show that VT may be associated with a wide range of symptoms that are not always severe or typical.

Methods

We interviewed 113 patients who were referred to our institution for management of VT. All had sought hospital treatment for what proved to be sustained VT of at least 30 minutes' duration. Patients who had VT associated with out-of-hospital cardiac arrest were excluded from this series, as were patients who had VT with acute myocardial infarction. In addition, patients with a known history of VT for which they were being treated with antiarrhythmic drugs were not

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included. In all cases, a wide-complex tachycardia was documented by an electrocardiogram, which was available for review. In 12 patients, the diagnosis of VT was based on the presence of independent atrial activity or fusion beats (or both) on the electrocardiogram recorded during the tachycardia. In the remaining 101 patients, clinical tachycardia was provoked during electrophysiologic testing by programmed ventricular stimulation and was shown to be ventricular in origin based on either the presence of atrioventricular dissociation or the absence of a His bundle depolarization preceding the ventricular depolarizations (or both of these) and the response to atrial and ventricular pacing during the tachycardia.

Patients were interviewed by one or more of the authors within a month of the episode of spontaneous VT and were questioned regarding their symptoms during VT. The patients were specifically questioned with regard to cerebral symptoms, chest pain, dyspnea and palpitations. In addition, histories obtained by physicians during the episodes of VT were reviewed to check for any discrepancies with the patients' responses.

All patients were examined by at least one of the authors. A diagnosis of congestive heart failure was based on the presence of a third heart sound gallop and a radiographic demonstration of cardiomegaly and pulmonary venous congestion.

Clinical Profile

The mean age of the patients was 57 ± 15 years. In all, 81 had coronary artery disease (with a history of myocardial infarction in 72), 10 had hypertensive heart disease, 7 had a congestive cardiomyopathy, 2 had isolated mitral valve prolapse, 1 had aortic regurgitation and 1 had undergone surgical repair of a tetralogy of Fallot. Eleven patients had no evidence of structural heart disease, with no abnormalities detected during physical examination, two-dimensional echocardiography or exercise treadmill testing.

Congestive heart failure was present in 58 patients (51%); 68 patients were being treated for supraventricular arrhythmias or ventricular premature depolarizations with quinidine sulfate, procainamide hydrochloride or disopyramide phosphate at the time they sought hospital treatment for VT, and 26 patients were being treated with propranolol hydrochloride for angina pectoris.

Statistical Analysis

Values are expressed as mean ± one standard deviation. The mean VT rates among the patients with syncope, near syncope, lightheadedness and no symptoms of cerebral hypoperfusion were compared using a one-way analysis of variance, with Cheffe's method for multiple contrasts. Other comparisons were done using either Student's t test or χ^2 analysis.

Results

The mean VT rate was 179 ± 37 beats per minute. There was no significant difference in the VT rate between patients who were and were not taking antiarrhythmic drugs (175 ± 37 beats per minute and 186 ± 36 beats per minute, respectively; $P > .05$).

Symptoms Related to Cerebral Hypoperfusion

In all, 17 patients had loss of consciousness, either persistent (10) or transient (7), in association with VT of a mean rate of 224 ± 29 beats per minute. Another 17 patients experienced near syncope and had a mean VT rate of 191 ± 38 beats per minute. Lightheadedness without syncope or near syncope was present in 40 patients in association with a mean VT rate of 170 ± 26 beats per minute. Of the 113 patients, 39 (35%) said they had no symptoms of lightheadedness, near syncope or syncope and they had a mean VT rate of 163 ± 31 beats per minute. A comparison of the VT rates among these groups of patients is shown in Table 1. The mean VT rate in the patients who had syncope was significantly greater than in the other groups of patients. In addition, patients with near syncope had a mean VT rate that was higher than that in patients who had no symptoms of cerebral hypoperfusion.

Patients with congestive heart failure had a significantly higher incidence of syncope than patients without congestive heart failure (Table 2). Within the group of patients who had syncope, there was no significant difference in the mean VT rate between patients with or without congestive heart failure. Patients without congestive heart failure more often had no symptoms of cerebral hypoperfusion than did those with congestive heart failure.

In comparing 35 patients who had a VT rate of 200 beats per minute or greater with 78 patients who had a VT rate of

TABLE 1.—*Cerebral Symptoms in 113 Patients Who Had Sustained Ventricular Tachycardia (VT)*

	Patients	*VT Rate*	
Symptom	*Number (%)*	*Beats/min**	P *Values†*
A Syncope	17 (15)	224 ± 29	A *v* B < .05 A *v* C < .001 A *v* D < .001
B Near syncope	17 (15)	191 ± 38	B *v* C NS B *v* D < .05
C Lightheadedness	40 (35)	170 ± 26	C *v* D NS
D None of the above	39 (35)	163 ± 31	

v = versus

*Mean ± one standard deviation.

†NS = not significant ($P > .05$).

TABLE 2.—*Cerebral Symptoms During Ventricular Tachycardia in 55 Patients With and 58 Patients Without Congestive Heart Failure (CHF)*

	Patients With CHF	*Patients Without CHF*
Symptom	*Number (%)*	*Number (%)*
Syncope	13 (24)	4 (7)*
Near syncope	6 (11)	12 (21)
Lightheadedness	21 (38)	19 (33)
None of the above	6 (11)	32 (55)†

*$P < .05$ (comparison of incidence of syncope among patients with and without CHF).

†$P < .001$.

TABLE 3.—*Cerebral Symptoms During Ventricular Tachycardia in 78 Patients With Heart Rate of Less Than 200 Beats per Min and 35 Patients With Heart Rate of 200 Beats per Min or More*

	Rate < 200 Beats/Min	*Rate ≥ 200 Beats/Min*
Symptom	*Number (%)*	*Number (%)*
Syncope	4 (5)	13 (37)*
Near syncope	8 (10)	10 (29)†
Lightheadedness	32 (41)	8 (23)
None of the above	34 (44)	4 (11)*

*$P < .005$.

†$P < .05$ (comparison of patients with rate < 200 beats/min versus those with rate ≥ 200 beats/min).

less than 200 beats per minute, the former more often experienced syncope or near syncope and less often had no symptoms of cerebral hypoperfusion than the latter (Table 3).

Other Symptoms During Ventricular Tachycardia

Chest pain during VT occurred more often in patients with coronary artery disease than in those without coronary artery disease (33% versus 12%, $P<.05$) (see Table 4). The incidence of dyspnea during VT was not significantly greater in patients who had congestive heart failure than in those who did not (33% versus 17%, $P>.05$).

Eight patients did not have symptoms of cerebral hypoperfusion or palpitations during VT. Five of the eight complained only of chest pain, one had shortness of breath, one only nausea and epigastric discomfort and one described his only symptom as being epigastric "fullness."

Illustrative Cases

Case 1. A 34-year-old woman who had mitral valve prolapse had noted two episodes of syncope over a period of a year. On the day of admission to hospital, she experienced an abrupt loss of consciousness for 10 to 15 seconds followed by a persistent sensation of near syncope. When she arrived at the emergency room, her blood pressure was 80/50 torr and heart rate 250 beats per minute. She said she did not have chest pain, dyspnea or palpitations. An electrocardiogram showed a wide-complex tachycardia at a rate of 250 beats per minute, which was terminated with direct-current countershock. The tachycardia was later provoked by programmed ventricular stimulation and was shown to be VT.

Comment. This case illustrates that sustained VT can cause a transient loss of consciousness, probably by initially causing an abrupt drop in blood pressure that is then partially reversed by reflex vasoconstriction. Another possible explanation in this patient is that the VT rate was initially faster than 250 beats per minute. Although her previous episodes of syncope and near syncope were in all likelihood caused by VT, she said she had no sensation of palpitations before or during the episodes. Therefore, the lack of palpitations does not exclude the possibility that cerebral symptoms are related to VT.

Case 2. The patient, a 64-year-old man with a history of myocardial infarction and congestive heart failure, came to the emergency room after having palpitations, mild shortness of breath and intermittent mild chest pain for two hours. His heart rate was 220 beats per minute and blood pressure 100/60 torr. He said he did not have any cerebral symptoms. An electrocardiogram showed a wide-complex tachycardia at a rate of 220 beats per minute, with atrioventricular dissociation. Carotid sinus massage was unsuccessful in terminating the tachycardia. The patient was then treated with intravenous administration of 10 mg of verapamil. Shortly thereafter, his blood pressure fell to 70 torr systolic, and he complained of near syncope and chest pain. The tachycardia was then terminated with direct-current countershock. During electrophysiologic testing, the tachycardia proved to be ventricular in origin.

Comment. The tachycardia was incorrectly diagnosed as supraventricular because of the patient's mild symptoms and well-maintained blood pressure. About 50% of patients in this series who presented with mild lightheadedness or no cerebral symptoms during VT were also incorrectly diagnosed as having supraventricular tachycardia for similar reasons. This led to inappropriate treatment with drugs such as verapamil, which in this case resulted in severe hypotension. This case shows that VT may at times be associated with mild symptoms even when the rate is more than 200 beats per minute and the patient has underlying congestive heart failure.

Case 3. The patient, a 62-year-old man with a history of myocardial infarction, had noted several episodes of nausea and epigastric discomfort lasting from 30 minutes to 3 hours over a period of six months. On one occasion, these symptoms persisted for several hours, at which time he went to a hospital. His heart rate was 160 beats per minute and blood pressure 110/60 torr. He said he had no symptoms other than nausea and epigastric discomfort. An electrocardiogram showed VT at a rate of 160 beats per minute. His symptoms of nausea and epigastric discomfort resolved after termination of VT by intravenous administration of lidocaine. When later undergoing electropharmacologic testing, his typical symptoms of nausea and epigastric discomfort were reproduced each time clinical VT was provoked by programmed ventricular stimulation.

Comment. This case shows how VT may at times cause atypical symptoms, in this case gastrointestinal symptoms.

TABLE 4.—*Symptoms (Other Than Cerebral) Experienced by 113 Patients During Sustained Ventricular Tachycardia**

Symptom	Patients Number (%)
Palpitations	64 (57)
Chest pain	31 (27)
Dyspnea	28 (25)
Weakness	7 (6)
Nausea	3 (3)
Diaphoresis	3 (3)
Flushing	2 (2)

*Some had more than one symptom.

Discussion

Although VT may often be a life-threatening arrhythmia requiring emergent treatment, the present series of selected patients who sought hospital treatment for what proved to be sustained VT shows that VT may be associated with a wide range of symptoms that are mild to severe. In this series, 69% of patients noted only mild lightheadedness or no cerebral symptoms at the time of hospital admission. About 50% of these patients were incorrectly diagnosed as having supraventricular tachycardia based on the absence of severe symptoms during the tachycardia. In several cases, this incorrect diagnosis led to inappropriate therapy with drugs aimed at the treatment of supraventricular tachycardia, such as digoxin or verapamil. In addition to delaying the onset of appropriate therapy, treatment with drugs such as verapamil may result in severe hypotension when administered intravenously to patients with VT. It is therefore important to recognize that VT may at times be associated with mild symptoms. The differentiation between supraventricular and ventricular tachycardia should be based on electrocardiographic criteria, not on whether or not a patient has severe symptoms during the tachycardia.

The severity of cerebral symptoms was at least partially

related to the rate of the VT—that is, patients with syncope had a higher mean VT rate than other patients and patients with near syncope had a higher mean VT rate than patients with no cerebral symptoms. In addition, patients who had a mean VT rate of 200 beats or more per minute had a 65% incidence of syncope or near syncope compared with only 15% among patients whose VT rate was less than 200 beats per minute. Nevertheless, it should be noted that 34% of patients who had a VT rate of 200 beats or more per minute had only lightheadedness or no symptoms of cerebral hypoperfusion during the VT. Patients with underlying congestive heart failure had a higher incidence of syncope during VT than did patients without congestive heart failure. This was the case even though there was no difference in the mean VT rate between these two groups of patients. Therefore, as would be expected, patients with depressed left ventricular function are less able to tolerate a given rate of VT.

Chest pain and dyspnea were each present in about a fourth of patients with VT. As might be expected, chest pain was more common in patients with known coronary artery disease. Although there was a tendency for dyspnea to be more frequent among patients with underlying congestive heart failure than in those without heart failure, the difference was not statistically significant.

Palpitations are often regarded as a classic symptom of paroxysmal tachycardia. In one report of 120 patients with paroxysmal tachycardia (supraventricular in 113), only 7% did not have palpitations.[21] However, in our series about a third of the patients with sustained VT did not have palpitations during the tachycardia. This observation has important implications regarding the evaluation of patients with unexplained syncope or near syncope. The lack of palpitations in association with these symptoms does not exclude the possibility that the symptoms are due to VT.

It is interesting to note that two patients had no palpitations, dyspnea, chest pain or cerebral symptoms during VT but complained of nausea or epigastric discomfort or both. Such symptoms in association with VT have been reported in a few patients.[15] Therefore, VT may rarely present with symptoms that are more gastrointestinal than cardiovascular.

In conclusion, it should be emphasized that the patients in this series are not a representative sample of all patients who have VT. In many patients VT may result in cardiac arrest and death. It is not our wish to minimize the malignant potential of VT but rather to highlight the observation that in a selected subgroup of patients who arrive at hospital with sustained VT that is not associated with cardiac arrest or acute myocardial infarction, it may be associated with relatively mild symptoms. The differentiation of supraventricular from ventricular tachycardia should be based on electrocardiographic criteria[22] and should not be influenced by whether a patient's symptoms are mild or severe.

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Indomethacin Therapy for Hypertrophic Pulmonary Osteoarthropathy in Patients With Bronchogenic Carcinoma

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Hypertrophic pulmonary osteoarthropathy (HPO) is a disabling complication of lung cancer often requiring thoracotomy with vagotomy for control of pain. This condition was confirmed by scintigraphy in six consecutive patients with biopsy-proved lung cancer. All had characteristic bone and joint pain unresponsive to a variety of analgesics. Treatment with indomethacin gave dramatic relief of pain within 72 hours in all six. Consideration should be given to instituting a controlled trial to establish the efficacy of indomethacin for the treatment of HPO.

(Leung FW, Williams AJ, Fan P: Indomethacin therapy for hypertrophic pulmonary osteoarthropathy in patients with bronchogenic carcinoma. West J Med 1985 Mar; 142:345-347)

Hypertrophic pulmonary osteoarthropathy (HPO) is a disabling complication of lung cancer often requiring thoracotomy with or without vagotomy for control of bone pain.[1] Six consecutively seen patients were treated with indomethacin for the pain of HPO. We report our experience and review the literature to offer a rationale for this form of therapy and, in addition, document the effect of indomethacin on the bone scan findings in cases of HPO.

Methods

Over a two-year period from 1979 to 1981, six patients presented to Wadsworth VA Medical Center with arthralgia, bone pain and abnormal findings on chest radiographs, diagnosed as HPO. The patients were treated with indomethacin. In addition to a history and physical examination, radiographs of the symptomatic extremities were taken, together with a radionuclide bone scan before treatment. Lung cancer was confirmed by bronchoscopic or aspiration biopsy. Treatment with indomethacin was initiated at 25 mg three times a day and increased to 50 mg three times a day if there was no symptomatic improvement after 24 hours. The bone scan was repeated in the last three of these six patients at 4, 12 and 16 days after starting indomethacin therapy. Follow-up data, including any change in arthralgia or bone pain, and the results of thoracotomy were recorded.

Results

These six patients were all men, aged from 46 to 62 years. Their smoking history ranged from 40 to 100 pack-years. Four had adenocarcinoma and two had epidermoid carcinoma of the lung. In four patients, the bone pain preceded the diagnosis of lung cancer by one to three months. In two patients, bone pain, pulmonary symptoms and abnormalities on a chest radiograph were recognized at about the same time. The most common bone symptom was a deep-seated ankle and shin pain reported by all six patients. Other joints frequently involved were the knees and the wrists. Clubbing of the fingers was present in five patients. Nonpitting edema of varying degrees over the involved joints was present in all six patients, and two had unmistakable knee effusions. Radiographs of the long bone showed characteristic periosteal elevations in five of the six. One patient had normal-appearing long bone on x-ray films. However, the bone scan was positive in all six patients (Figure 1).

Before admission, analgesics, including aspirin, acetaminophen or codeine, were tried by these patients, with only minor relief of bone pain. These treatments were not repeated in hospital. Two patients were treated with 25 mg and four patients with 50 mg of indomethacin given three times a day. Significant relief of bone pain occurred within 24 hours in two, 48 hours in another three and 72 hours in the sixth patient. The bone scan was repeated in the last three of these

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six patients at 4, 12 and 16 days after starting indomethacin therapy. All three repeat bone scans remained positive. Five patients underwent exploratory thoracotomy. Four underwent resection of lung tumors. Vagotomy was not done in any patient. All five patients had resolution of bone pain after thoracotomy, so that therapy with indomethacin did not need to be restarted. The one patient not operated on was treated with radiation therapy. Bone pain persisted and continued use of indomethacin was necessary.

Discussion

In this uncontrolled study of six consecutive patients with HPO due to lung cancer, indomethacin in doses of 25 to 50 mg three times a day rapidly and completely controlled the disabling bone pain. There is indirect evidence that prostaglandins may be involved in the pathogenesis of this condition. The plasma concentrations of prostaglandins $F_2\alpha$ and E are significantly higher in cystic fibrosis patients with digital clubbing than in those without clubbing.[2] In vitro organ culture studies have shown that prostaglandins can cause an increase in number and activity of osteoclasts[3] and an increase in bone resorption.[4] In vivo, both are prerequisites to the new bone formation that is the hallmark of HPO.[5] Indomethacin was chosen for study because it has been shown to inhibit such new bone formation in a variety of conditions, perhaps as a result of prostaglandin synthesis inhibition,[6] such as Haversian remodeling in rabbits,[7] ectopic ossification after a hip operation,[8] fracture healing in rats[9] and bone resorption in periodontitis in dogs.[10] In addition, there are several anecdotal reports of the effective use of indomethacin in cases of HPO.[11-13]

The documented efficacy of other analgesics such as aspirin,[14] which is also a prostaglandin synthetase inhibitor, further supports the possibility that prostaglandins may be important in the pathogenesis of the pain symptom of HPO. A double-blind controlled study would be desirable to firmly establish the efficacy of this treatment in patients with HPO. Whether this treatment may be useful as a diagnostic tool in the evaluation of long bone pain in which radiographic evidence of periostitis is absent deserves further study. In practice, complaints of long bone pain are common in conditions such as osteomalacia, discogenic disease, soft tissue rheumatism, infections and venous insufficiency, but in general such pain does not respond to indomethacin therapy as rapidly as in patients with HPO. The rapid relief of pain noted in this study could be used to raise the possibility of HPO, and the diag-

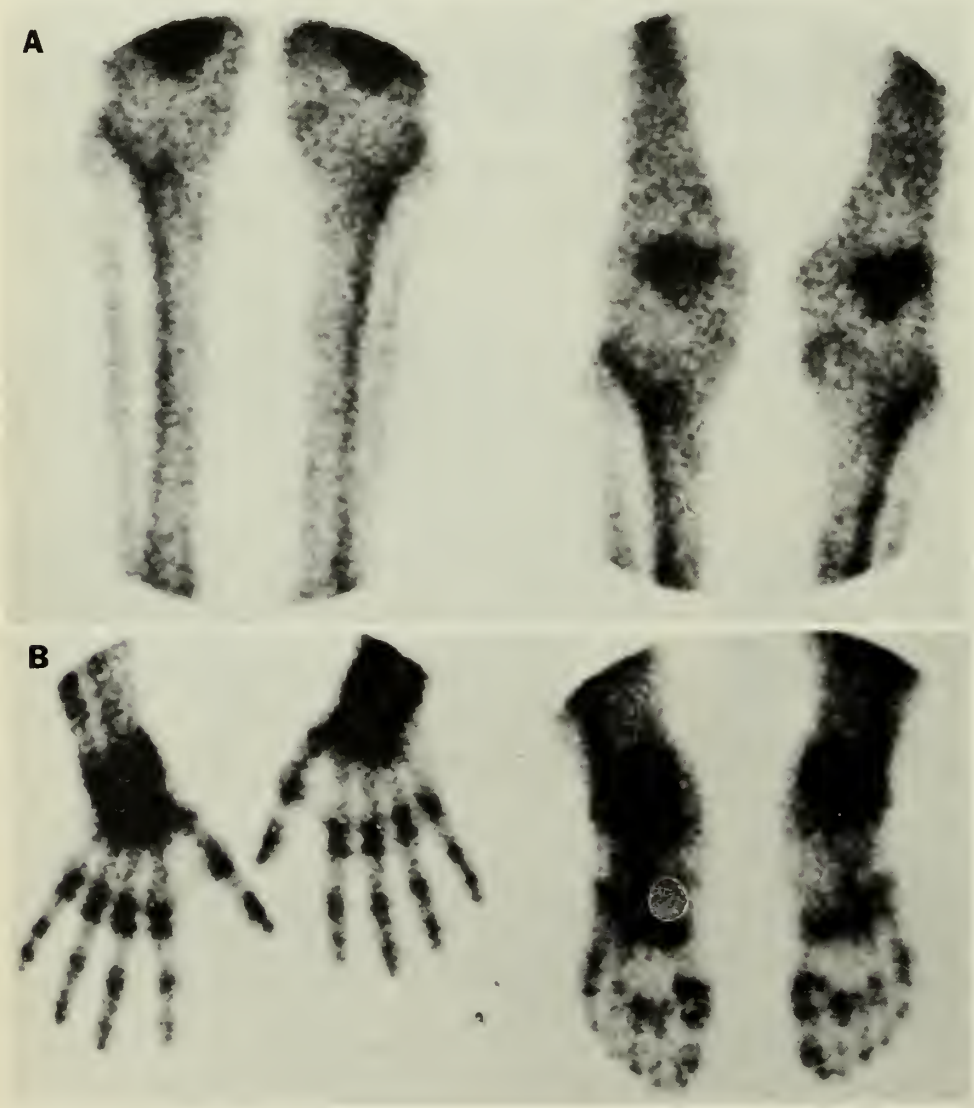

Figure 1.—A, radionuclide bone scan of part of the femur and tibia showing diffuse, symmetrically increased cortical uptake of technetium Tc 99m medronate (the "parallel tract" sign). **B,** Similar scan of the hands and feet, with considerable uptake in wrists, ankles and digits.

nosis then would be confirmed easily by bone scan. Bone scanning has been shown to be more sensitive than routine bone radiographs in recording the full extent of skeletal involvement,[15,16] though it has not been recommended as a diagnostic tool. The results have been shown to revert to normal one month after appropriate treatment of a lung tumor or metastasis, whereas bone radiographs continue to show abnormalities[16-18] and we were interested to further define the time course of this change. In this study, bone scans were uniformly positive, confirming the sensitivity of the test. In this situation bone scans may allow an earlier diagnosis of HPO and consequently an earlier search for an occult lung cancer. There have been reports of bone scan findings returning to normal 1 to 12 months following definitive treatment of a case of lung cancer. In our experience, however, the scans that were repeated within two weeks showed findings that were unchanged.

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Congenital Tracheal Occlusion in Neonates—A Minireview

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Congenital tracheal occlusion, though seemingly rare, is generally fatal if not attended to immediately. A high index of suspicion should help to make the diagnosis in a neonate when there are respiratory distress at birth and no audible cry and an endotracheal tube cannot be advanced beyond the vocal cords. We present our experience with cases of congenital tracheal obstruction due to various causes during a period of four years.

(Sankaran K, Bhagirath CP, Duncan WJ, et al: Congenital tracheal occlusion in neonates—A minireview. West J Med 1985 Mar:142:348-351)

Congenital occlusion of the trachea is rare. If the problem is misdiagnosed, the invariable result is death of the newborn. Most of the infants previously described with congenital tracheal occlusions have survived for a few minutes to several days only. At the University Hospital, Saskatoon, during a period of four years ending December 1983, we have managed seven cases with congenital tracheal occlusions. Our objective in this paper is to review these cases and to deal with congenital tracheal occlusion as a separate disorder because in previous reports it was included with proximal upper airway occlusions, such as those of the oropharynx or larynx, and distal airway occlusions, such as bronchial and pulmonary agenesis.

Patients and Methods

Hospital records of infants admitted to the Neonatal Intensive Care Unit (NICU), University Hospital, Saskatoon, with the diagnosis of congenital tracheal occlusion were examined. During a period of four years ending December 31, 1983, a total of 2,920 infants were admitted. Of these infants, seven were identified as having congenital tracheal occlusion, presenting with immediate neonatal respiratory distress. The details of each case are given below. This tertiary-care center for sick neonates serves northern and central Saskatchewan, with 10,000 to 12,000 live births per year. The details of cases 1 and 2 have been described previously.[1,2]

Reports of Cases

CASE 1. Briefly, the patient, a baby boy, was born spontaneously at 36 weeks' gestation. The antenatal history included premature rupture of membranes and evidence of polyhydramnios. The infant was limp and cyanotic at birth. Attempts to intubate the trachea and oxygenate the child failed because the endotracheal tube would not pass beyond the vocal cords. Immediate tracheostomy improved the baby's condition dramatically. Later investigations confirmed the presence of proximal esophageal atresia, tracheal atresia just below the vocal cords and evidence of a tracheoesophageal fistula distally. The tracheoesophageal fistula was repaired on the first day of life. The atretic area of the trachea was resected at 1 month of age, and a stent was put in place. The stent had to be removed six weeks later, however, because of granulation tissue. At 2½ years of age, the infant is doing well with a tracheostomy. Bronchoscopy shows an opening of approximately 3 mm at the site of resection. Both physical and neurologic development of the baby are near normal for postconceptional age.

CASE 2. The patient, a female infant, was born by cesarean section 24 hours after the infant of case 1. The mother was at 36 weeks' gestation with a history of polyhydramnios. The infant at birth had no audible cry, was cyanotic and was in respiratory distress with pronounced indrawing. Attempts at intubation failed because the endotracheal tube would not pass beyond the vocal cords. An immediate tracheostomy resulted in remarkable improvement. As with case 1, investigations showed proximal esophageal and tracheal atresia with a distal tracheoesophageal fistula. The fistula was repaired immediately and, unlike the previous case, repair of the tracheal atresia was deferred to a later time. The infant is now 2½ years of age and doing remarkably well, her development

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ABBREVIATIONS USED IN TEXT

CT = computed tomographic (scan)
NICU = Neonatal Intensive Care Unit

being normal, except for language skills, for her postconceptional age. Surgical correction is planned at about 4 to 5 years of age.

Case 3. The patient, another term male infant, was born to a 21-year-old gravida 1, para 0 mother in a local hospital outside of Saskatoon. The mother received no antenatal care. Polyhydramnios was noted at the time of delivery. The baby was cyanotic despite pronounced respiratory effort and indrawing. Intubation was attempted twice, but again the endotracheal tube could not pass beyond the larynx. The infant died at 2 hours of age. Autopsy showed proximal esophageal atresia and a distal tracheoesophageal fistula with complete occlusion of the lumen of the larynx by a bar of cartilage immediately below the level of the vocal cords. A histologic section at the area of occlusion on the trachea showed a hairlike lumen lined with respiratory epithelium. No other congenital abnormalities were noted. Interestingly enough, this patient was born a month after the infants in cases 1 and 2 with the same abnormalities.

Case 4. This female infant was born to a 24-year-old primigravid woman at 34 weeks' gestation in a breech presentation and of a breech delivery. An ultrasound study done at six months' gestation showed evidence of oligohydramnios and polycystic kidneys. The membranes ruptured at delivery and oligohydramnios was noted. Immediately after birth the baby showed respiratory distress, and attempts to pass an endotracheal tube failed. The Apgar scores were 5 at one minute and 0 at five minutes. An autopsy showed agenesis of the trachea along with agenesis of both lungs, the right kidney, ureter, urinary bladder and uterus. Other anomalies included a polycystic left kidney, an atrioseptal defect, polysplenia and a patent ductus arteriosus.

Case 5. The patient, a male infant, was born to a 28-year-old gravida 2, para 1 mother at 32 weeks' gestation. An ultrasound study done antenatally showed oligohydramnios. The infant presented at birth with severe respiratory distress. Apgar scores were 1 at one minute and 0 at five minutes. An autopsy showed tracheal agenesis with agenesis of both lungs and polycystic kidneys.

Case 6. This male infant was born to a 27-year-old gravida 2, para 2 mother by spontaneous vaginal delivery at term with no antenatal problems. The infant was cyanotic and grunting immediately after birth with a severe degree of indrawing and inspiratory wheeze. Apgar scores were 3 at one minute and 7 at five minutes. The infant was intubated with some difficulty by the transport team and taken to the NICU. A slight occlusion was noted in passing the endotracheal tube below the vocal cords. Later, extubation resulted in severe inspiratory stridor and cyanosis. An esophagogram, a computed tomographic (CT) scan of the neck and a chest x-ray film showed no abnormalities. Bronchoscopy showed narrowing of the lumen of the trachea below the vocal cords, suggesting an extrinsic compression and a severe degree of tracheomalacia at the site of the obstruction. Angiogram showed a partial vascular ring with an anomalous origin of the common carotid artery. Surgical suspension of the aortic arch was done in an attempt to relieve the extrinsic compression on the trachea. This produced no improvement. Tracheostomy was done to maintain ventilation. The plan is to remove the tracheostomy after six months following bronchoscopy. The infant is now 6 months old and there are no abnormalities on physical and neurologic examinations.

Case 7. The patient, a male infant, was born at 36 weeks' gestation, weighing 1,650 grams, to a 24-year-old primigravid mother by cesarean section. Antenatal history was unremarkable except for breech presentation and a history of smoking, averaging half a pack a day through the pregnancy. Apgars were 4 at one minute and 8 at five minutes, and the baby required endotracheal intubation and ventilation. There was some difficulty noted in passing the tube beyond the vocal cords. The neonatal course was complicated by continual respiratory distress and evidence of congestive heart failure. Cardiac catheterization showed a patent ductus arteriosus, ventricular septal defect, dextrocardia and a prominent, high aortic arch causing tracheal compression. Bronchoscopy showed evidence of an extrinsic compression of the trachea. A surgical procedure was done to suspend the aortic arch and ligate the patent ductus arteriosus, with immediate improvement of respiratory state. Further investigations, such as bronchography, CT scan of the trachea and repeat bronchoscopy, showed significant stenosis of the entire trachea. Eventually, the baby was discharged at 10 months of age with minimal respiratory distress. He is normal physically and neurologically at 2½ years of age.

Discussion

The incidence of congenital tracheal occlusions at our center is about 1 in every 420 admissions. In other words, an approximate incidence of 1 in 5,000 to 7,000 live births is noted in the province of Saskatchewan. From our experience, congenital tracheal occlusion presents in three different forms: intraluminal—such as tracheal atresia, laryngeal web and failure to canalize the trachea—extraluminal due to external compression—that is, cystic hygroma, vascular rings, annular thyroid and the like—and tracheal maldevelopment, such as agenesis of the trachea and lungs.

Of the seven cases described above, three showed similar abnormalities. Two of these three babies recovered without sequelae. The third infant, even though he had a similar history, did not recover for two reasons. First, he was born at a small hospital where there were no facilities for immediate intervention and, second, the attending physicians were not sensitive to the problem. Because there was a hairlike lumen through the atretic area, the lungs were filled with air but there was inadequate gas exchange. The infant must have died of increasing acidosis, hypoxia and hypercapnia. The above cases have clearly shown that immediate intervention may be lifesaving. To our knowledge, these two infants are the first ever to have survived similar abnormalities beyond the neonatal period. Only one case with similar lesions has been reported before. This was diagnosed at autopsy.[3] The reason for clustering is still unknown. All investigations to elucidate this occurrence were unfruitful.

In the fourth and fifth cases, it was obvious that there was no palpable trachea, and this was associated with multiple congenital anomalies and oligohydramnios. Autopsy has confirmed anomalies inconsistent with sustained life.

The sixth case was one of aortic arch anomalies and associated tracheal occlusion and tracheomalacia at the site of occlusion. Again, the immediate neonatal presentation showed evidence of acute respiratory tract occlusion and difficult intubation. Tracheostomy was done to sustain the airway patency. The tracheomalacia due to compression is expected to resolve with time. Secondary tracheomalacia develops in those instances in which the tracheal wall has been subjected to chronic external pressure.[4]

The seventh case had tracheal stenosis and compression. As the infant grows, there will be relative abatement in the respiratory difficulty. This was confirmed by continued improvement observed in this case.

Congenital tracheal occlusion may occur when there are compressive extrinsic or intrinsic lesions of the trachea or tracheal maldevelopment. The extrinsic causes include cystic hygroma, goiter, tumors and vascular anomalies. Cystic hygroma is a cystic tumor of lymphatic tissue that frequently arises in the neck and may rapidly attain large size due to hemorrhage or infection. It may extend proximally into the floor of the mouth and distally into the mediastinum.[5] Congenital goiter is rare but usually seen in infants of mothers who have consumed large quantities of medication containing iodides during their pregnancy. In rare cases it can be large enough to cause respiratory obstruction at birth.[5]

Mediastinal cysts and tumors may produce acute respiratory occlusion at birth. Diagnosis is established radiologically, and the lesions may be differentiated by their position in the chest. Neurogenic tumors are usually in the posterior mediastinum—goiter and thymoma—and in the anterosuperior mediastinum; bronchogenic and esophageal duplication cysts are most frequently located in the hilar area, whereas the teratodermoid group of tumors is found in the anteroinferior mediastinum.[5]

The primary vascular malformations producing airway occlusion in infants are abnormalities of the aortic arch and its derivatives. Persistence of a vascular segment that would normally regress or abnormal regression of a portion that would normally remain patent may produce a vascular ring—this ring then causing occlusion of the trachea, esophagus or both.[6] The existence of symptoms depends, of course, on the relative tightness of the ring. The severity of the symptoms may vary from dysphagia to reflex apnea—so-called dying spells caused by tracheal occlusion.[7]

Of the four vascular lesions, three deserve discussion—double aortic arch, anomalous innominate artery and aberrant left pulmonary artery.

Of the patients with double aortic arch, 75% have symptoms varying from stridor with wheezing to dyspnea and cyanosis. Symptoms are made worse with crying and especially with feeding of solid foods. Diagnosis rests with angiography and the treatment is surgical.

The average age at surgical treatment is 8 months. About 95% of cases of double aortic arch involve division of the smaller persistent left aortic arch and left ligamentum arteriosum.[8]

A low-lying anomalous innominate artery can cause anterior tracheal compression. This group of patients suffers most from reflex apnea (16/23 in Toronto). Bronchoscopy will show the anterior tracheal compression as a pulsatile mass. The majority, 86% of these patients, have been treated conservatively[9] (Macdonald and Fearon, 1971) with gradual improvement. Persistence of reflex apnea requires surgical suspension of the innominate artery to the sternum, which provides nearly complete relief of symptoms.

If the pulmonary artery branch of the embryologic left sixth aortic arch fails to develop, a collateral branch from the right aortic arch then develops to supply the left lung, producing the very rare "aberrant" left pulmonary artery.[8] This vessel passes between the trachea and esophagus. The aberrant left pulmonary artery causes expiratory stridor in newborns as opposed to inspiratory stridor from the other types of rings. Diagnosis rests with angiography and simultaneous barium swallow. Treatment involves surgical repositioning of the aberrant left pulmonary artery.

The intrinsic causes of tracheal occlusion include subglottic hemangioma or, very rarely, lymphangioma and laryngeal webs. The diagnosis may be suggested by asymmetric narrowing of the trachea on chest x-ray film, but it should be confirmed by direct observation using endoscopy.[10] Case 7 exemplifies this point.

Tracheal anomalies such as stenosis, atresia and agenesis can present with respiratory tract occlusion at birth. Some of the lesions are amenable to immediate treatment, as evident in cases 1 and 2, whereas others are not. Atresia refers to congenital absence or closure of a normal opening, passage or cavity in the body, while agenesis refers to complete or almost complete failure of the anlage of an organ to develop. Severe cases of tracheal atresia often have been grouped with cases of tracheal agenesis.[11,12] We have classified cases 1 and 2 as tracheal atresia as we were unable to locate any opening on repeated bronchoscopies. Obviously, case 3 will be classified as severe stenosis or atresia, whereas case 7 has severe stenosis of the trachea. About 40 cases have been reported with tracheal atresia, agenesis or both in the literature.[12–15] Most had a tracheoesophageal or a bronchoesophageal fistula and, in several cases, surgical intervention was attempted.[15–18] All died eventually, with the longest survival being six weeks.[18]

The management of tracheal occlusion depends on awareness of the problem and prompt recognition. After it is established that an infant has acute respiratory tract occlusion and not respiratory depression, the airway should be cleared and a gentle attempt at ventilation should be tried. If intubation is unsuccessful, with difficulty encountered in advancing the endotracheal tube beyond the larynx, consideration should be given to immediate tracheostomy. The following features should alert attending physicians to immediate intervention: severe respiratory distress without audible cry, antenatal polyhydramnios or oligohydramnios, failure to advance an endotracheal tube beyond the vocal cords and palpable distal trachea. Once an airway is established, management will depend on the cause of the occlusion. Most cases will require surgical intervention at a later date.

In summary, physicians dealing with newborns must be familiar with the causes of acute tracheal occlusion in a neonate. Prompt diagnosis and proper management may help salvage some of these infants.

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The Athletic Health Care and Training Program

A Comprehensive Approach to the Prevention and Management of Athletic Injuries in High Schools

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The Athletic Health Care and Training Program was developed to meet the educational, organizational and record-keeping needs of the interscholastic athletic program of the Seattle Public Schools. The program components were the education of coaches, school nurses and student trainers; development of a centralized training room; implementation of written procedures, and establishment of a record-keeping system. At the end of the three-year study period, schools involved in the program were better prepared to handle emergencies than were control schools. Schools involved in the program were found to have an injury-recognition rate comparable to that previously reported for high schools that had athletic trainers, a rate substantially higher than that in the control schools. The experimental schools were judged to have managed these injuries satisfactorily 95% of the time, compared with a satisfactory management rate of 14% for the control schools.

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In a federal study reported in 1979,[1] it was estimated that nearly 600,000 injuries were sustained by 5 million male and female participants in high school interscholastic sports during the 1975-1976 school year. Approximately 15% of these injuries resulted in more than three weeks of time lost. While interscholastic sports have traditionally involved primarily male athletes, participation by women has grown steadily in the past decade. In 1975-1976 more than a million women played varsity sports and incurred 100,000 injuries.[1]

Several studies[2-6] have shown that high school coaches and student athletes are not adequately trained in basic principles of athletic health care, namely injury recognition, treatment, rehabilitation and prevention. Calvert[1] reported that 77% of high schools identified a coach as the source of athletic health care; however, only 53% of these coaches have had adequate training for these responsibilities. Moreover, 11% of public high schools and 15% of private secondary schools have athletic trainers on their staffs, but only 5% of athletic trainers are certified by the National Athletic Trainers Association (NATA).[1]

At the high school level, there has been no system of recommended procedures or guidelines for the students, parents and coaches who must initially cope with most sports-related injuries.[3-5,7] In a Nebraska study in 1981, Conley[8] noted that 70% of high schools surveyed did not even have an emergency transportation policy. Moreover, there has been little effective communication and coordination among those responsible for maintaining an athlete's health. It is not surprising that even when proper decisions are made by an athlete's personal doctor regarding injury management, the instructions are often carried out incorrectly or not at all. This lack of communication and inadequate attention to detail were noted in the Nebraska study, which indicated that 75% of schools do not have a follow-up care policy in force.[8] Another significant shortcoming of high school athletic programs has been the failure to maintain meaningful records that can be used to follow an injured athlete's progress and ensure that the athlete returns to play only when it is safe to do so.

Both the lack of basic health care information and the absence of a systematic administrative approach are central to the problems experienced by high schools in preventing and managing injuries. Others have recognized these deficiencies

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ABBREVIATIONS USED IN TEXT

DOE = Department of Education
NATA = National Athletic Trainers Association

and have created models for understanding the steps required to formulate a program for preventing and managing injuries.[9,10] While the educational needs have begun to be addressed, few of the organizational and managerial needs have been implemented at the secondary school level.

The Athletic Health Care and Training Program was developed as a model pilot program at the Division of Sports Medicine, University of Washington, to provide a comprehensive health care program to meet the educational, organizational and record-keeping needs of the interscholastic athletic program of the Seattle Public Schools.[11] The program was funded under Title IV-C, Elementary/Secondary Education Act, US Department of Education (DOE). The program was validated by the Joint Dissemination Review Panel of the DOE on July 21, 1982. The program has been part of the National Diffusion Network since November 1983. In this paper, we report the methods used in implementing the program and the data obtained during the evaluation of it.

Methods

Components

The interventions of the program were (1) to create a "health care team" by educating coaches, student athletic trainers and school nurses; (2) to develop a centralized training room operated by student trainers under adult supervision; (3) to implement a series of written guidelines, protocols and procedures for daily use by the health care team in preventing and managing injuries for athletes in all sports, and (4) to use record-keeping forms that facilitate sharing information with parents, personal physicians and other members of the health care team.

Population

In all, 16 high schools (12 public and 4 private or parochial) composed the Seattle Metropolitan League. None of the 16 schools had a functioning centralized training room, an educational training program for coaches, a system of athletic record keeping, properly outfitted first-aid kits or appropriate sideline emergency equipment. Seven schools were initially selected in 1978 by the athletic coordinator of the Seattle Public Schools for participation in the program. Five schools completed implementation of the program. A lack of administrative commitment on the part of two schools was the principal reason for failure of implementation. Each of these five experimental schools participated in parts of the evaluation. Four schools were selected as controls for various parts of the evaluation from among the nine schools that were not chosen for participation in the program. A comparison of the five experimental schools and the four control schools showed that the two groups were similar with regard to enrollment, faculty size, athletic participation and the composition of the coaching staff.

Evaluation

To evaluate the effects of the various program interventions, specific objectives reflecting outcomes were developed. Several instruments to measure these outcomes were created specifically for this purpose.

The specific objectives of the program were as follows:

- *Training.* The coaches, student trainers and school nurses who complete the 27 classroom-hour training course would have increased knowledge of athletic health care principles and practices based on pretest and posttest results.
- *Emergency preparedness and pre-event protocols.* Experimental schools would have emergency preparedness and use pre-event procedures to a greater extent than would control schools.
- *Injury recognition.* Experimental school coaches would have a greater ability to recognize injuries than control school coaches.
- *Postinjury protocols.* Experimental schools would more closely follow appropriate postinjury procedures than would control schools.

Financial limitation of the grant necessitated that only some of the schools could be evaluated for each objective. All five experimental schools and all four control schools were involved in at least one part of the evaluation.

Measurement of Educational Outcome

The training course for coaches, school nurses and student trainers consisted of 27 hours of lectures, slide presentations, demonstrations, videotapes and laboratories. A 300-page text was prepared to augment the classroom teaching. The course covered four areas: (1) "prehabilitation"—those preventive measures carried out before the first competition, such as screening, conditioning, nutrition guidelines, equipment fitting, safety measures and emergency preparedness; (2) injury management, including recognition, first-aid treatment, referral to a personal doctor, rehabilitation and definition of criteria for return to play; (3) athletic trainer skills—laboratory sessions covering taping, wrapping, use of heat and ice and equipment modification, and (4) health system organization, including record keeping, communications and standardization of written guidelines and protocols.

A 72-item multiple-choice cognitive test was used as a pretest and a posttest for all coaches, school nurses and student trainers to evaluate the educational gains from the training course. A KR-20 reliability coefficient of internal consistency was determined for the examination. The validity of each question was confirmed by three faculty members from the Division of Sports Medicine. To measure whether pretesting had an effect on posttest outcome, one class of coaches and one class of student trainers took the course without a pretest. A *t* test for related means was applied to determine the statistical significance of the pretest to posttest differences within each group. A *t* test for unrelated means was applied to compare the test results of coaches, school nurses and student trainers.

Measurement of Behavioral Changes

- *Emergency preparedness and sideline safety activities.* The availability and adequacy of first-aid kit contents, sideline supplies, sideline emergency equipment, preevent warm-up activities and sideline safety activities were monitored and recorded by two trained observers. These on-site observations were made at least once for all sports at three experimental schools and at three control schools during the 1979-1980 school year. During each observation the pres-

ence or absence of 51 items or activities was assessed. Each item of the first-aid kit and each component of the sideline supplies and emergency equipment were given a weighted value from 1 to 5, depending on their importance to emergency preparedness or injury prevention (Table 1). The scores for the first-aid kit items (20 items) were added separately from the scores for the components of the emergency equipment and sideline supplies (ten items). The nonparametric Wilcoxon test, which uses comparisons of the sum of ranks, was applied to both data sets.

Each of the pre-event warm-up activities and sideline safety activities was analyzed separately by a χ^2 test.

• *Injury recognition.* All experimental and control schools were required to complete and submit a monthly injury report form for each sport during the 1980-1981 school year. All 16 schools in the Seattle Metropolitan League had been voluntarily using this monthly injury report form for each sport during the 1979-1980 school year. All coaches received an annual in-service session on proper use of the form during the preseason meetings of coaches. Comparison of the 1979-1980 record keeping from experimental and control schools showed similar compliance in the proper use of the form.

An injury was defined as a medical problem resulting from athletic participation that required an athlete be removed from a practice or competitive event or miss a subsequent practice or competitive event. A day lost to injury was any day in which the athlete was not able or not permitted to participate in an unrestricted manner. Time lost to injury was expressed as the number of practices and games (rather than calendar days) the athlete missed or participated in on a limited basis. Significant injuries were defined as those that limited participation for five or more practices and games, major injuries as those that limited participation for 15 or more practices and games.

Injury rates were expressed as injuries per 100 athletes per season and as injuries per 1,000 athletic exposures. An athletic exposure was defined as any practice or game in which an athlete had an opportunity to be injured. The total team athletic exposures for a season were obtained by adding the number of athletes participating each day.

Data from the 1980 football injury reports from three experimental schools and two control schools were analyzed by a χ^2 test and a test of significance between two independent proportions.

• *Injury management.* A case study technique was developed to evaluate sports injury management. A comprehensive interview format was used to provide information on an injured athlete. Football injuries were studied at the same five high schools that provided the injury recognition data. All athletes who missed a game or practice during October 1980 and were at school on the day when the data collector visited were interviewed. Interviews were conducted retrospectively after the football season. In all, 38 cases from three experimental schools and 21 from two control schools were examined. Data were collected on each injury from the time of occurrences through all phases of treatment, rehabilitation and return to play. A graduate student in health education was trained to collect the data through structured interviews with the injured athlete, the football coach and student trainers.

Objective criteria for evaluating injury management were developed in conjunction with certified athletic trainers. A ten-page explanation detailing these criteria was provided to each evaluator, along with a scorecard for grading each case (Figure 1).

Four time periods were considered: the period immediately after recognition of the injury (day 1); a later time on the same day in the training room or locker room (day 1); the time period between the day of injury recognition and the day of return to play (day 2 through day X), and the day of return to play (day X plus 1). Within each time period, four activities were evaluated: examination and assessment; first aid, ongoing treatments and rehabilitation; communication with parents and personal doctors, and record keeping. In addition, initial injury recognition and transport to the sideline and locker room were studied.

The data from each interview were summarized in narrative form. The case study narratives were evaluated by 11 physicians and 2 university athletic trainer-therapists who were unaware of which high school an injured player attended. An overall score of pass or fail was affixed to each case by the 13 evaluators based on specific judgments regarding health care performance for each activity within the various time periods. A test of significance between two independent proportions was applied to the data from experimental schools and control schools.

TABLE 1.—*Sideline Observation Check Lists and Point Values*

First-Aid Kit Items

Category/Item	*Point Value*
Emergency	
Athlete identification cards	4
Directions to hospital	3
Coins for telephone	3
Oral airway	3
Flashlight	2
Taping	
Adhesive tape	4
Underwrap	3
Scissors/tape cutters	3
First aid	
Band-Aids	3
Gauze pads	3
Elastic wraps (Ace)	3
Skin lubricant	3
Ointment	2
Alcohol	2
Eyewash	1
Miscellaneous	
Cotton balls	1
Cotton-tip applicators	1
Finger splint	1
Tissues	1
Tongue blades	1

Emergency Equipment/Sideline Supply Components

Water	5
Ice in plastic bags	3
Ice chest	2
Crutches	3
Sling	3
Air splints	2
Stretcher	2
Towels	1
Knife/Phillips screwdriver (football only)	3
Bolt cutters (football only)	3

Results

Educational Outcome

The reliability coefficients for four separate classes showed a pretest range of 0.71 to 0.78 and a posttest range from 0.86 to 0.96. These results indicate a high level of test reliability.

The pretest and posttest results for participants in the training courses are shown in Table 2. The 169 coaches, 24 school nurses and 130 student trainers all showed statistically significant increases in cognitive gains ($P < .001$). The improvement was approximately twice the standard deviation for each group.

The 23 coaches and 50 student trainers who took courses without a pretest had posttest means, standard deviations and ranges that were not significantly different ($P > .05$) from the posttest means of those who took the pretest (Table 2). These data indicate that taking a pretest did not influence the outcome of the posttest.

In all, 14 student trainers attended the course a second time one year later and retook the pretest and posttest (Table 3). The posttest mean score for these student trainers after taking the course a second time was not significantly different from the posttest mean scores of either the coaches or the school nurses. The knowledge loss over the year from the first posttest to the second pretest (2.75%) was not statistically significant. Student trainers showed significant gains in knowledge each time the course was taken ($P < .001$). The percentage gain for these student trainers from the first pretest to the second posttest was 28.54%.

Behavioral Changes

• *Sideline observations.* The results from the on-site observations for all sports from three experimental and three control schools showed that the experimental schools were better prepared than the control schools (Table 4). The scores that reflected the contents of the first-aid kits from the two groups of schools were significantly different ($P < .005$) based on a 20-item list (Tables 1 and 4). Similarly, the two groups of schools differed significantly ($P < .01$) in the availability of other sideline supplies and emergency equipment based on a ten-item list (Tables 1 and 4).

Sideline observations monitoring preevent activities and safety precautions during practices and games were also made. A χ^2 test used to compare the data from the experimental and control schools showed that the experimental schools did significantly better ($P < .01$) than control schools with regard to each of the following items: preventive taping, the use of proper technique for static stretching before activity, stretching as a team activity rather than as an individual activity, the presence of ice in plastic bags in an ice chest at

TABLE 2.—*Test Results of the Educational Courses for Coaches, School Nurses and Student Trainers*

		Pretest			*Posttest*			*Difference*		
Group	*Number*	$\bar{X}$(%)	*SD*	*Range*	$\bar{X}$(%)	*SD*	*Range*	*Mean Gain (%)*	*SD*	*Significance (P Value)*
Coaches	169	55.06	9.02	33-76	72.59	9.44	44-94	17.53	8.19	< .001
	23*	. . .	. . .	. . .	74.00	8.70	50-90	. . .		
School nurses	24	60.08	7.16	45-75	75.75	9.32	50-93	15.67	8.84	< .001
Student trainers	130	42.38	8.67	14-63	64.64	10.47	28-91	22.26	8.52	< .001
	50*	. . .	. . .	. . .	63.75	11.86	28-84	. . .		

$\bar{X}$ = mean; SD = standard deviation.

*Did not take pretest.

CASE STUDY SCORECARD CASE # _____ EXAMINER _____

	IMMEDIATE CRISIS Field + Sideline or Time First Reported	SAME DAY: POST CRISIS Locker/Training Room after Game or Practice	TREATMENT-REHABILITATION From First Day After the Injury until the Day of Return to Play	RETURN TO PLAY Decision and Actions about Participation	TOTAL
Injury Recognition					
Transport	To sideline	To training room			
Examination-Assessment (History, Physical exam and diagnosis)	Initial exam	Re-examination inside	Progress assessments	Clearance exam	
First Aid + Treatments	At sidelines	Inside training room Also - to go home	Protocols + Modalities	To permit safe play Equipment Adjustment Taping	
Communication-Advice	Parents/Doctor Actions at home	Parents/Doctor Actions at home	Doctor visit; Coach contact with doctor	Doctor's clearance Coach contact to doctor	
Record Keeping	Daily Injury Report Note to Doctor/Parent	Daily Injury Report Note to Doctor/Parent	Doctor's note Forms-Treatments, Team Doctor, Injury Report	Doctor's clearance note; Daily Injury Report	
TOTALS					

Figure 1.—Case Study Scorecard.

TABLE 3.—*Test Results of Student Trainers Who Completed Educational Course Twice*

Group	Number	Pretest $\bar{X}$(%)	Pretest SD	Pretest Range	Posttest $\bar{X}$(%)	Posttest SD	Posttest Range	Difference Mean Gain (%)	Difference SD	Significance (P Value)
First course	14	45.82	6.24	35-57	65.89	10.29	51-85	20.07	9.67	<.001
Repeat course	14	63.14	9.50	50-81	74.35	9.50	60-85	11.21	7.50	<.001

$\bar{X}$=mean; SD=standard deviation

TABLE 4.—*All Sports Sideline Observations for Presence of Emergency Items*

	First-Aid Kit Score		Sideline Supplies/ Emergency Equipment	
	Experimental	Control	Experimental	Control
Number of schools	3	3	3	3
Number of observations	115	73	115	73
Sum of ranks	12,121	5,645	11,792	5,974
Mann-Whitney U statistic	2,944		5,122	
Z score	3.45		12.55	
Significance level	$P<.005$		$P<.01$	

the sidelines and the presence of student trainers before and during activity.

• *Injury recognition.* The injury report data from the 1980 football season are shown in Table 5. The reported frequency of injuries at the experimental schools was significantly higher than that at the control schools ($P<.001$). When expressed as injuries per 100 participants per seasons, the experimental schools reported nearly three times more injuries than control schools. When the rates were normalized to injuries per 1,000 athletic exposures, the rate was 2½ times greater at the experimental schools ($P<.001$).

The anatomic locations of the football injuries were generally similar between experimental and control schools, with 53% of experimental (E) and 45% of control (C) injuries to the lower extremity, 14% of E and 15% of C to the hip and torso, 28% of E and 24% of C to the upper extremity and 4% of E and 15% of C to the neck and head.

The severity of injuries differed for the experimental and control schools (Table 5). The median time loss for each injury was three practices and games for experimental schools and five practices and games for control schools. The percentage of total injuries classified as significant and major injuries was significantly higher ($P<.01$) for the control schools than for the experimental schools.

• *Injury management.* The case studies were collected from the same three experimental and two control schools that were used to provide the injury recognition data (Table 5). The sample size was 22% of all the football injuries from the experimental schools for the 1980 football season and 57% of the football injuries from the control schools. The results showed that 36 of 38 cases (95%) from experimental schools received a majority of passing grades for injury management, whereas only three of 21 cases (14.3%) from control schools received a majority of passing grades from the 13 reviewers (Z statistic=6.25; $P<.001$). In 50 of the 59 cases (85%), the agreement on pass-fail results was 10 to 3 or more. Evaluation was unanimous (13 to 0) in 25 cases. When minor injuries (one day only) and major injuries (15 or more games and practices) were removed from the case study analysis, a majority of passing grades was shown in 2 of 17 (12%) cases from control schools and in 20 of 22 (91%) cases from experimental schools ($P<.001$).

The control schools did progressively worse than experimental schools in all aspects of injury management as the time after injury increased. First aid, communications and record keeping were the activities in which these deficiencies were most pronounced. Record keeping was the activity in which the difference between the experimental and control schools was the greatest, followed by communication and first-aid management. Experimental schools more frequently followed procedures that the evaluators deemed desirable athletic health care than did control schools.

Discussion

The study showed that it was possible to implement a comprehensive and systematic program of athletic health care in high schools. An important measure of success was the behavioral changes that took place following training. The application of knowledge in emergency preparedness and in warm-up and sideline safety activities was more important than the mere acquisition of such knowledge. All sports were assessed in the sideline observation portion of the evaluation; hence, the significance of the difference between experimental and control schools indicated improvement in those areas for the entire athletic program, not just football.

Differences in injury rates arise in part from differences in the definition of an athletic injury. Because of our interest in examining injury recognition, we chose a definition that provided the highest sensitivity. Thus, our definition of an athletic injury was that used by Garrick and Requa,[12] which included all injuries resulting in any restriction in participation, including those injuries resulting in restricted participation only on the day of the injury.

Differences in injury rates also occur as a result of the method of reporting injuries. Two studies of high school football injuries in North Carolina, which used different methods of coach reporting, identified rates of about 40 to 55 injuries per 100 participants per season.[13,14] The Seattle study of Garrick and Requa,[12] conducted during the mid-1970s, identified injuries by placing an NATA-certified athletic trainer in each of four high schools. The injury rate for football in the Seattle study was 81 injuries per 100 participants per season. In the present study the control schools had a football injury rate (26.9 per 100 participants per season) similar to most of the studies using the coach-reporting method. The experimental schools had an injury rate (79.8 per 100 participants per season) similar to the rate reported when athletic trainers were present in the schools.

It seems unlikely that the implementation of an educational program and organized system of injury management resulted in a doubling of injuries. Rather, the difference was more likely related to a higher rate of injury recognition by experi-

TABLE 5.—*Football Injuries Reported by Coaches for 1980**

	Experimental	*Control*	*Significance (P Value)*
Number of schools	3	2	. . . .
Average squad size	71	69	. . . .
Injury rate/100 athletes/season	79.8	26.8	. . . .
Injury rate/1,000 athletic exposures	17.3	6.9	<.001
Median time loss/injury (games and practices)	3.0	5.0	. . . .
Mean time loss/injury (games and practices)	5.1	9.2	<.001
Significant injuries/total injuries (%)	29.0	54.0	<.001
Significant injuries/100 athletes/season	23.5	14.5	. . . .
Significant injuries/1,000 athletic exposures	5.1	3.7	<.01
Major injuries/total injuries (%)	8.0	24.0	<.01
Major injuries/100 athletes/season	6.1	6.5	. . . .
Major injuries/1,000 athletic exposures	1.3	1.7	NS

NS=not significant

*Significant injury = time loss of 5 or more games and practices; major injury = time loss of 15 or more games and practices.

mental schools. More than half (54%) of the injuries at control schools resulted in a time loss of five or more practices and games compared with 29% at experimental schools ($P<.001$). By comparison, in the Seattle study[12] in which certified athletic trainers reported injuries, 31% of football injuries resulted in more than five days of time lost. The experimental schools' shorter average time loss may reflect both recognition of minor injuries and better management of moderate injuries, two factors that can be expected to decrease time loss.

Record keeping has rarely been considered an important part of high school athletic health care, while certified trainers at the university and professional level routinely maintain such records. As Conley reported in the Nebraska survey,[8] less than 25% of high schools have a follow-up care policy *in force*. Examples of such a policy include establishing guidelines for referral to a physician, requiring a written note from the physician specifying the diagnosis and treatment plan, ensuring that arrangements for rehabilitation of an injury are made and requiring written clearance from a physician before the athlete is permitted to return to participation. Attention to detail through record keeping, as shown in the case studies, helped to ensure that the guidelines and procedures that are intended for implementation were in fact being carried out.

Perhaps the simplest and most direct way to manage athletic health problems in high schools would be to place an NATA-certified trainer in each high school.[6,7,15,16] This solution is not currently practical because there are 20,000 secondary schools and fewer than 5,000 certified trainers. The presence of a certified trainer does not in itself answer all of the athletic health care needs of high schools, because the trainer cannot always be present where athletes are participating. There still would be a need for educated coaches and student trainers who *are* present at all practices and games. Coaches are directly responsible for all aspects of their interscholastic athletic teams, including the management of the athletic health care.

The keys to successfully instituting an adequate health care system for high school athletics are the recognition that a problem exists and an administrative commitment to make the needed changes on a schoolwide basis. Reliance on a voluntary change in behavior by individual coaches after participation in an educational program is fraught with uncertainty. Calvert[1] noted that the attention of coaches generally focuses on the practice or competition itself, rather than on health care problems. An organized approach that offers a coach some assistance from other trained persons (student trainers, school nurses, adult trainers) in meeting these responsibilities would be more likely to yield satisfactory outcomes in preventing and managing injuries.

This study has shown that a comprehensive and systematic program of athletic health care for high schools can be implemented and evaluated. Institution of the Athletic Health Care and Training Program in Seattle area high schools resulted in significant educational gains; favorable behavior modifications relating to preparedness for emergencies and injury; recognition of injury and management of injuries, and improved cooperation, communication and record keeping. This program is available for dissemination to high schools throughout the nation via the National Diffusion Network of the US Department of Education.

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Psychosocial Events and Subsequent Illness—A Review

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The public readily accepts the relationship between psychosocial events and illness and acknowledges that stress is important in the acquisition of disease. However, scientific documentation of these relationships has not been convincing and many clinicians remain skeptical. In this review we survey selected studies from socioepidemiologic, psychologic and physiologic research, chosen for their methodologic rigor, that help clarify the relationship between psychosocial events and illness. We conclude (1) though difficult to prove, available data support a positive relationship between psychosocial events and illness, and (2) psychologic well-being is important for good physical health.

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Through socioepidemiologic, psychologic and physiologic research, we have seen in the 20th century innumerable theories generated in support of the relationship between psychosocial events and illness. Yet most physicians fail to acknowledge the reliability of this relationship. Indeed, those authorities most familiar with the subject cite several major deficiencies in stress research that invalidate many of its conclusions.[1] These include the failure of researchers to adopt or apply a consistent definition for psychosocial stress, the inappropriate application of results from animal studies to human events and the failure of researchers in this field to control for many other possibly influential variables.

Despite these shortcomings, valid scientific information is available that adds clarity to the relationships between psychosocial factors and the development of selected diseases. The purpose of this review is to provide the reader with an overview of relevant studies, selected for their valid scientific design, that utilize socioepidemiologic, psychologic and physiologic variables to relate psychosocial events to the onset of disease. More information is drawn from research on cardiovascular disease because it most closely meets the ideal design standards.

Definition of Stress

Psychosocial stress is an umbrella term under which is included almost every way in which society, environment, culture, personality, behavior or emotion might influence a person. For practical purposes, psychosocial stress can be defined as an organism's response to those external factors or stimuli (stressors) that demand some reaction or change in behavior.[2] While stress produces a state of disequilibrium in an organism, it cannot yet be measured directly. Thus, its effects are assessed indirectly, through sociocultural, psychologic and physiologic data. For example, among populations, a change in social status whether upward or downward, or incorporation into or exclusion from a cultural environment, are considered stresses.

For an individual person, stress is most often defined in three ways. In psychologic terms, it is a recognizable emotional response such as anxiety or depression precipitated by an unpleasant, threatening or harmful event. Because anxiety and depression are clinical entities that can be measured in standardized fashion, it becomes possible to measure stress in psychologic terms. Another commonly used method involves the study of life-change events; the theory proposes that stress results from a person's attempt to adjust to various life events, for instance, change in employment or the death of a spouse. Because data have been collected showing that certain of these life events elicit quantitatively similar responses among large groups of people, such events have been assumed to impose equivalent levels of stress on different persons. A third way to measure stress is in the change of some physiologic variable

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thought to be related to the development of disease (for example, rise in blood pressure or increase in catecholamine output).

Population and Sociocultural Research

In a number of sociocultural and epidemiologic studies, the presence of psychosocial factors predisposing select population groups to the premature development of disease has been discussed. Two large epidemiologic studies offer evidence in support of the role of psychosocial factors in the acquisition of coronary artery disease among American populations.

Gordon and colleagues studied rates of coronary artery disease in three large populations: those in Framingham, Massachusetts; Honolulu, Hawaii, and Puerto Rico. Their results showed that the sum of known risk factors for coronary artery disease was inadequate to account for either the prevalence or incidence of the disease in the study populations.[3] In addition, coronary artery disease was twice as prevalent and became clinically manifest four times more often for the Framingham population than for those in Honolulu or Puerto Rico, even though there was striking similarity among the populations with respect to standard risk factors. In another study, Keys and co-workers developed highly complex statistical formulas that predicted the risk of acquiring coronary disease for Europeans. They then applied these formulas to American populations and found that Americans had a twofold unexplained risk for coronary disease over their European counterparts, even when all usual risk factors were considered.[4]

From these and similar studies of large populations there emerges the concept that in certain countries, sociocultural influences are independent risk factors for coronary artery disease. Unfortunately, in none were sociocultural variables studied per se, so that any conclusion can only be speculative as to their role in coronary artery disease.

Information that relates coronary disease to other sociocultural factors, such as social mobility, social attainment and social disruption, shows conflicting results. In a large cross-sectional investigation, Syme and associates reported a higher incidence of coronary artery disease among white collar workers born in the urban United States who had changed careers several times or had moved often to another geographic area when age and traditional risk factors were controlled for.[5] Geographic mobility was an important factor in the development of new coronary disease in a prospective study from Israel of middle-aged men.[6] Shekelle and colleagues, in a prospective study of an industrial population of middle-aged men, showed that the risk for coronary artery disease was greater if social class in childhood was higher or lower than the one currently experienced.[7] From these and similar studies, one might conclude that a person who frequently moves and changes jobs, crosses social class lines and is concerned with social status is at increased risk for coronary artery disease.

However, there is much evidence to the contrary. A five-year prospective study investigating the relationship between occupation, education and coronary disease among 270,000 employees in the Bell System showed that men who attained the highest rank of management did not have a higher risk for coronary disease than men who remained at lower levels. In addition, there was no evidence that the coronary disease rate for employees who had high levels of responsibility, who were promoted frequently or transferred to new departments or companies was greater than for those who did not undergo these changes.[8] One of the few factors that predicted increased risk for disease was low educational achievement. In addition, a cross-sectional epidemiologic analysis of the incidence of coronary artery disease for the middle-aged male labor force of an industrial corporation found no difference among sociologic subgroups defined by occupation, income and education.[9]

Further support for a negative correlation between occupational attainment and coronary disease comes from the results of a 40-year review of 17,530 middle-aged London civil servants.[10] The age-adjusted prevalence of coronary disease was significantly higher among those at the lowest employment grade when compared with those at the top. Some, but not all, of the difference could be explained by the usual risk factors.

In spite of some of these apparent contradictions, there is more consistent evidence that new adaptation to Western cultural standards may be a risk factor for the development of coronary artery disease. In a large sociocultural study of Japanese men living in different environments, the incidence and prevalence of coronary artery disease were lowest in Japan, intermediate in Hawaii and highest in California.[11] Again, the differences remained significant after accounting for traditional risk factors. When specific sociocultural risk factors were sought to explain the differences among Japanese living in California, relevant findings emerged. For those with Western life-styles, the prevalence of coronary disease was three to five times greater than for those with Japanese styles.[11]

These sociocultural studies reflect some of the problems of stress research. Each study was large, controlled and prospective, but conclusions appear to be somewhat inconsistent and contradictory. A partial explanation for the inconsistencies in conclusions may relate to unrecognized differences in variables, such as study sample size or ethnicity of the subjects.

Similarly, epidemiologic data that relate sociocultural factors to hypertension and cerebrovascular disease are inconclusive. There is plentiful information for hypertension, consistent with the thesis that a significant rise in blood pressure results from acculturation into Western society. It has not been possible thus far to eliminate several other reasonable alternative explanations for observed differences—body weight, state of general health and salt intake.[12] For studies of cerebrovascular disease, incomplete demographic and sociocultural data collection, retrospective reviews, life events information provided by biased informants and the absence of control groups make the available information virtually meaningless.[13]

Behavioral and Psychologic Studies

In contrast to the contradictions and inconsistencies of socioepidemiologic information, data supporting a relationship between behavioral and psychologic factors and the premature acquisition of certain diseases are more convincing.

Friedman and Rosenman initially suggested that certain behavioral traits, which they termed the type A personality, might be important for the acquisition of coronary disease.[14]

They included an overly aggressive, driving and demanding style and an inordinate sense of time consciousness. These characteristics were subsequently evaluated prospectively in a five-year study in which 1,990 middle-aged men without coronary artery disease were screened with both the Minnesota Multiphasic Personality Inventory and a questionnaire evaluating 16 personality factors. Subjects in whom coronary disease later developed were (1) more independent in social relationships, (2) more suspicious about the motives of others and (3) had greater feelings of inner tension than those in whom coronary artery disease did not develop.[15]

The most definitive attempt to confirm these relationships evolved from the Western Collaborative Group study, which included more than 3,000 middle-aged men employed by ten companies. In addition to traditional intake information, individual behavior patterns were classified as type A or B by a standardized, previously validated interview. This 8½-year study showed a clear and independent relationship between the incidence of coronary heart disease and type A behavior.[16]

Anxiety and depression have been extensively used as psychologic measures of psychosocial stress. Several carefully carried out studies show an association between chronic anxiety and depression and coronary disease. In a prospective study of 1,300 graduates of the Johns Hopkins Medical School, Thomas and Greenblatt showed that early morning fatigue as a symptom of depression was more often present in those subjects who later suffered a myocardial infarction than in those who remained healthy.[17] In a prospective English study of 2,000 patients and an equal number of matched controls, Eastwood and Trevelyan found that new coronary artery disease was much more likely to develop in those who responded positively to questions about chronic mild anxiety and depression than in controls.[18]

Medalie and colleagues, in a prospective study of 10,000 Israeli men, showed that anxiety over problems and conflicts in areas of finance, family and co-workers were associated with 2½ times the risk for the development of angina pectoris; the intensity of the anxiety and not its specific content seemed to be the critical factor.[6] Although not conclusive, these carefully designed prospective studies strengthen the hypothesis that higher levels of anxiety, depression and dissatisfaction with life may well increase the risk for coronary artery disease.

Evidence from behavioral and psychologic data for the role of psychosocial factors in the development or maintenance of hypertension is less clear. In 1955 Wolf and coworkers reported the results of a large prospective study that showed that emotional factors and life stress were significantly related to hypertension, but no specific stress events or behavioral characteristics were identified.[19] Some recent studies using life events or life change units as measures of stress have failed to show any reliable relationship between level of stress and essential hypertension.[20] In addition, the Johns Hopkins Precursor Study has thus far failed to demonstrate any relationship between psychological or behavioral factors and the development of hypertension.[21]

Others have shown a positive correlation, however. The perceived stress of adverse working conditions and the prevalence of hypertension in a group of industrial workers was studied by House and colleagues.[22] They evaluated completed questionnaires that sought information about work conditions and job satisfaction. After controlling for known risk factors, hypertension was shown to be associated with job dissatisfaction. Theorell has recently shown that a combination of psychologic and social dimensions is important in the establishment or maintenance of hypertension whereas neither alone is related.[23] In a prospective study of 5,000 middle-aged Swedish men in the construction industry, substantial recent life change along with significant job dissatisfaction correlated with both systolic and diastolic hypertension. Those with high scores in only one area were not at increased risk.[23]

Two psychologic and behavioral characteristics have been emphasized as important for the subsequent development of cancer: the first is repressed feelings of loss, denial and depression; the second is behavior characterized by inflexibility and conformity.[24,25] In a prospective evaluation of a group of women with known class III Papanicolaou smears, those subjects who had a recent history of loss or who displayed hopelessness were at significantly greater risk to have cancer subsequently diagnosed than those who did not manifest these feelings.[26] Greer and Morris evaluated behavior patterns in 160 women admitted to hospital for breast biopsy and showed that these abnormal emotional states were statistically more common among those who were subsequently diagnosed as having cancer.[27] In a longitudinal evaluation of students from the Johns Hopkins School of Medicine, those in whom cancer developed from 17 to 32 years after the study was done had maintained less closeness to their families as youths than those students in whom cancer did not develop.[28] Finally, Shekelle and colleagues, in a 17-year prospective study of 2,020 middle-aged employed men, reported that subjects with depression identified at entry examination had twice the risk of subsequent death from cancer.[29] The association did not vary appreciably when adjusted for age, smoking, alcohol use, family history or occupational status.

An early study examining the relationship of psychosocial stress and infection was designed to identify those factors that might be responsible for the acquisition of β-streptococcal pharyngitis and nonstreptococcal respiratory infections in 16 families (100 persons).[30] Each family kept a diary of events and each member of the study had specimens for throat cultures taken routinely every three weeks and at the time of an acute illness for a period of one year. On the basis of a previously arranged scale, the diaries were reviewed and events independently interpreted as psychologically stressful or not. Those considered stressful were then compared for their timing in relation to the onset of infections. The results showed that it was four times as common for an infection to be antedated by a stressful event as to be followed by one. When individual family chronic stress scores were compared with four independent variables of streptococcal disease (acquisition rates, prolonged carrier states, streptococcal illness rates and antistreptolysin 0 responses), there was a definite increase in all variables with increasing stress.[30]

Bartrop and associates compared in vitro lymphocyte responses with antigenic challenge for 26 bereaved spouses and controls; for the former there was a tenfold depression of lymphocyte function at five weeks after the precipitating event. Although no other immunologic dysfunction was found, the groups were not controlled for medications or other illness.[31]

Two recently published longitudinal studies relating psychosocial events to subsequent illness through behavioral and psychologic data are free of many of the uncontrolled variables that compromise other studies and deserve special comment.

The Johns Hopkins Precursor Study, to which reference has already been made,[17,21,28] used a strictly defined study population—sophomore medical students, the vast majority of whom were single, white men, all of whom were adjudged physically and mentally normal. The goals of the study were to identify psychologic indexes that might be important for the subsequent development of disease. For a cohort of medical students in 17 successive classes between 1948 and 1964, a broad range of psychological characteristics ("habits of nervous tension") was recorded. Subsequently, physical and mental health was evaluated yearly by a questionnaire. Periodically, these "habits of nervous tension" have been quantified and compared between those subjects in whom serious disease developed, or who died, and those who have remained healthy. Data for five disorders have been examined: suicide, cancer, hypertension, myocardial infarction and mental illness.

By 1980 almost 1,350 subjects had been included. Of these, myocardial infarction had developed in 20, hypertension in 53, some form of cancer in 55, some mental illness severe enough to require admission to hospital in 31 and 10 had committed suicide. Significantly higher levels of depression, anxiety and anger under stress were present for those who later had coronary artery disease, mental illness or who committed suicide as compared with those who remained healthy.[17,21,28]

The importance of mental health for physical well-being has recently been confirmed in the Grant Study of Adult Development, a prospective study of the natural history of psychologic health in men.[32]

The methodologic advantages of this study were several: mental and physical health, at outset normal, was studied prospectively; information was collected in a blinded fashion; other social and biologic variables, including socioeconomic status, smoking, culture, quality of medical care, parental longevity, obesity and alcoholism were controlled for through multiple regression analysis. In 1942, 204 college men were selected. Of these, 185 remained in the study and in good health until 1964. Of that group, 100 continued to be in excellent physical health through 1975; 54 acquired minor problems and in 31 serious chronic illnesses developed or they died. When the group was divided into those with the best and those with the worst mental health from entrance until 1964, there were substantial differences in the acquisition of serious illness or death between the two groups during the next 11 years. Only 3% with the best, but 38% with the worst mental health became chronically ill or died.

Neuroendocrine Data

The development of a neuroendocrinologic theory to explain stress-related events has been attempted by many investigators, but few unifying concepts have emerged.

Selye theorized that the hypothalamic-pituitary-adrenal axis is the primary neuroendocrine system influenced in certain types of chronic stress. He proposed that when a psychosocial stress is perceived by an organism and when normal coping mechanisms fail to control it, the organism reacts with depression.[33] He observed that in both animals and humans these conditions were associated with increased adrenocorticotropic hormone (ACTH) and corticosterone or cortisol release. Thus, Selye reasoned that certain stresses stimulated the limbic system, which triggered the hypothalamic-pituitary-adrenal axis, resulting in increased release of ACTH and corticosteroids and, in the long term, their pathophysiologic sequelae. In both animals and humans there is abundant evidence that ACTH levels increase with arousal, especially in situations that a person interprets as uncontrollable.[34]

Additional evidence has accrued to support the theory that psychologic events alter the pituitary-adrenal axis. Sachar has shown that a significant number of patients with depression have an altered adrenal-pituitary axis.[35] In these persons, patterns of cortisol secretion are very different from normal. The number of cortisol pulses is increased and plasma cortisol levels are elevated over those for normal controls both at the beginning and the end of a 24-hour cycle, with a general flattening of the entire curve. Abnormal responses to dexamethasone suppression have been reported in between 40% and 50% of these patients, while normal suppression is seen in about 98% of matched controls.[35-37] With improvement of the clinical depressive state, both normal dexamethasone responsivity and cortisol circadian activity reappear. For this reason some investigators argue that primary depression results in a chronically abnormal hypothalamic-pituitary-adrenal axis.

Excess ACTH secretion has also been proposed to explain the relationship between psychosocial stress and infection and cancer. Using mice, Riley has shown that stress, whether produced by psychosocial or mechanical factors, results in increased corticosterone output and increased rates of spontaneous tumor formation and tumor growth.[38] In theory, these secondary effects of increased corticosterone output involve changes in T cells, B cells and natural killer cells—all of which impair normal host immune surveillance and increase susceptibility to oncogenic virus acquisition and tumor growth.

The validation of either of these models, however, requires evidence of chronic alteration of the pituitary-adrenal axis. Currently there is no consensus that long-term hypersecretion of ACTH and corticosterone or cortisol can be attributed to psychosocial stress.[39,40] Most studies that have monitored the adrenocortical response to chronic stress have shown very rapid adaptation and return of ACTH to normal levels.[13] To explain ACTH hypersecretion in cases of primary depression, it now appears that a defect may reside in brain noradrenergic or serotonergic receptor activity. Recently available neuropharmacologic data show that in the intact brain, norepinephrine exerts a tonic inhibition of ACTH secretion. Thus, cortisol hypersecretion in depressed patients may reflect disinhibition of corticotropin-releasing hormone secretion because of relative brain catecholamine depletion, not a primary neuroendocrine abnormality.[41]

In contrast, there is stronger evidence for a relationship between chronic catecholamine hypersecretion and certain stresses. Early in this century, Cannon hypothesized that an animal would increase adrenomedullary output when a psychologic or psychosocial stress was perceived as a threat to its control (flight or fight response).[42] Subsequent workers hy-

pothesized that these responses originate from the amygdaloid regions in the limbic system and activate the sympathetic-adrenomedullary axis. When these responses become chronic because of the organism's lack of adaptation, excess plasma catecholamines are elaborated, as eventually are their pathophysiologic sequelae—such as hypertension, lipoprotein abnormalities and coronary artery disease.

The results of early work supported the existence of selective adrenergic responses to emotional stimulation: anger resulted in higher levels of norepinephrine and anxiety in higher levels of epinephrine.[43] Although these studies were much criticized, recent work has confirmed these findings.[13,44,45] In addition, it appears that increased catecholamine output may be chronically maintained. For example, Timio and associates evaluated a group of workers whose jobs fluctuated between periods of extreme and minimal time stress.[46] While oxygen consumption rates remained unchanged during both periods, norepinephrine and epinephrine levels rose twofold and fourfold, respectively, during stressful work. In addition, these differences persisted each time they were measured over extended periods.[46]

Several investigators have reported a positive correlation between heightened values for urinary catecholamines and certain behavioral attitudes, such as constant striving for achievement and the need to control a situation, or particular personality or body types.[13,44] Friedman and co-workers showed that norepinephrine levels rise among type A relative to type B persons when both are challenged by the same mental contest,[47] and urinary catecholamine values for the type A group are elevated over the type B group during a normal workday.[48] Urinary catecholamine excretion is elevated in both healthy volunteers and patients with known coronary disease during urban automobile driving, but more significantly for the patients.[49] For survivors of myocardial infarction who then periodically completed a schedule of recent events survey and had simultaneous urine catecholamine levels measured, there was significant correlation between degree of stress and increased urinary epinephrine values.[50]

Discussion

Although currently available information does not allow us to make comprehensive statements about psychosocial events and subsequent illness, some reasonable conclusions can be offered. In the Adult Development Study, there is a very clear relationship between continued mental wellness and physical well-being. In those subjects who had the poorest mental health predictably more physical disease developed over the ensuing decade than in those with better mental health. In the Johns Hopkins Study, those medical students who manifested traits of psychologic stress in their youth subsequently suffered increased incidences of coronary artery disease, mental illness and suicide. While these conclusions are based on a very narrowly defined segment of the population, they may have more far-reaching implications.

In reference to psychosocial risk for coronary artery disease, some definite statements can be made. Epidemiologic data from population studies allow for the presence of an independent psychosocial risk factor for coronary heart disease, but do not identify it. Sociocultural data provide conflicting conclusions and, at present, are best interpreted with caution. For recent immigrants, adaptation to Western culture may be an exception and likely is a firm sociocultural risk for coronary disease. The clearest association is between behavior and coronary artery disease, for which there is abundant support. Finally, individual characteristics of anxiety and depression may be independent risk factors for coronary heart disease for which there are also supportive neuroendocrinologic data.

Transitory rises in blood pressure resulting from psychologic and psychosocial factors have been extensively documented. However, the relationship between these factors and essential hypertension remains much less clear. Although it is probable that sociocultural and even psychologic risk factors for hypertension are operative, the inability to account for or control the other variables makes the identification of these factors nearly impossible.

To explain both increased susceptibility for cancer and increased rates of infection through psychosocial stress, the neuroendocrine model that proposes chronic overstimulation of the hypothalamic-pituitary-adrenal axis is attractive. Abundant experimental findings in animals relate the acquisition of cancer to the immunosuppressive effects of ACTH. There are also data in humans to relate depression to increased risk for cancer, and there are physiologic data showing that a predictable group of patients with primary depression will have chronically elevated ACTH and cortisol levels resistant to dexamethasone suppression. However, there is no human information, to date, relating long-term alteration of the pituitary-adrenal axis to psychosocial events. The abnormal ACTH and cortisol levels in patients with primary depression seem best explained by deficient brain amine-receptor activity. Similarly, the hypothesis that increased rates of infection may be related to individual stress is attractive; yet, there are only a few scientifically sound human studies, from which no firm conclusions can yet be drawn.

From the evidence available at this time, it seems that the best advice the physician can offer patients is that good mental health is important for maintaining physical well-being. In dealing with patients and their concerns, physicians should bear in mind the adage that Sir William Osler popularized almost a century ago:

It is not nearly as important what disease a patient has—as what patient has a disease.[51]

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Medical Progress

Intracavitary Chemotherapy for Malignant Disease Confined to Body Cavities

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The direct administration of cytotoxic chemotherapeutic agents into the peritoneal or pleural cavities to treat malignant disease principally involving these regions is based on modeling studies suggesting a major pharmacokinetic advantage for the exposed cavity compared with the plasma. The safety and clinical efficacy of several agents administered directly into body cavities either singly or in combination have now been shown. Additional studies are needed to define optimal drugs, dosages and treatment schedules for the various tumors confined to body cavities. Whether this form of therapy will prove to be superior to standard systemic drug administration will require controlled clinical trials comparing the two treatment methods.

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While the systemic administration of chemotherapeutic agents will result in satisfactory delivery of drug to well-vascularized regions of the body, there is legitimate concern that this approach to the delivery of cytotoxic therapy might not be optimal for tumors confined to body cavities. To improve the efficacy of therapy for malignant disease in the pleural and peritoneal cavities, investigators have attempted to administer drugs directly into the region being treated. While *intracavitary chemotherapy* has frequently been used as a method to produce sclerosis and prevent reaccumulation of malignant effusions, recent modeling studies have suggested that this might be an excellent approach to the delivery of drugs administered for their cytotoxic properties.[1] Following a brief discussion of sclerosing therapy, I will highlight some of the major principles of intracavitary chemotherapy and will conclude with examples of the potential utility of this modality in patients with malignant disease principally confined to body cavities.

Intracavitary Chemotherapy Administered for Its Sclerosing Properties

The administration of chemotherapeutic agents directly into body cavities is not a new concept. In the early days of the medical use of alkylating agents, mechlorethamine hydrochloride, a nitrogen mustard, was instilled into the peritoneum of patients with malignant ascites in an effort to kill tumor and prevent fluid accumulation.[2] Initial reports suggested significant reductions in the rate of ascites formation following treatment with mechlorethamine, hemisulfur mustard and thiotepa administered by the intracavitary route.[2-4] While the investigators involved in these early studies suggested that the alkylating agents were directly cytotoxic to cancer cells, there was little evidence of shrinkage of any mass lesion, and it is much more likely that the drugs were acting as *sclerosing agents*. Pain was often severe in patients receiving intracavitary chemotherapy and, as a result, this form of therapy became reserved for patients with recurrent pleural effusions and intractable ascites.

Several chemotherapeutic agents have shown major utility in controlling malignant effusions. While mechlorethamine is used less often today because of the pain it produces, the agent is effective in controlling the reaccumulation of pleural effusions in as many as 40% of patients treated.[5,6] The use of bleomycin sulfate has produced complete and partial response rates in controlling pleural effusions of 60%.[7,8] Patients with effusions due to breast carcinoma appear to respond more favorably than patients with lung cancer. The agent is less effective in preventing the reaccumulation of ascitic fluid. Local pain and fever are the most frequently reported side effects. Several different dose schedules of bleomycin have been effective in inducing sclerosis, with the optimal dose being 60 units in 100 ml of saline.[8]

Doxorubicin hydrochloride has also been a useful agent in inducing sclerosis in the pleural and peritoneal cavities and in preventing fluid reaccumulation.[5] In one study, 12 of 15 patients (80%) with effusions responded to the intracavitary

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ABBREVIATIONS USED IN TEXT

NCI = National Cancer Institute
UCSD = University of California, San Diego

administration of doxorubicin, with three patients having complete clearance of fluid for a minimum of two months. The dose of doxorubicin administered in this study was 30 mg in 25 ml of normal saline.

While the optimal management of malignant effusions and ascites has not been clearly defined, the administration of several chemotherapeutic agents or tetracycline[9] directly into the body cavity to be treated has been at least partially effective palliation in about 50% to 60% of patients treated.[10] The major toxic effect is usually local pain. This can frequently be decreased by the simultaneous administration of lidocaine along with the sclerosing therapy. Drainage of as much fluid as possible before instilling the drug is an important principle in assuring the best possible result of therapy and chest tube drainage both before and after the administration of chemotherapy is frequently done.

Effective treatment regimens for sclerosis of body cavities use *high* concentrations of drug in *small* treatment volumes. This contrasts sharply with the basic principles of intracavitary therapy for the delivery of chemotherapeutic agents administered for their cytotoxic properties, as will be discussed further.

Principles of Intracavitary Chemotherapy Administration

The first and one of the most important steps in the ability of a chemotherapeutic agent to kill a malignant cell is delivery of the drug to the tumor in the highest concentration possible. As previously mentioned, drugs administered systemically have access to well-vascularized organs such as the bone marrow or gut. Because of longer diffusional distances, however, it is likely that chemotherapeutic agents given intravenously will have much lower penetration into extravascular cavities, such as the pleural space, peritoneal cavity and central nervous system. From theoretic modeling a major possible pharmacokinetic advantage has been suggested for drugs administered directly into body cavities.[1] While the details of such mathematical modeling studies are beyond the scope of this review, the basic principles they define are important to understand the rationale behind direct intracavitary administration of chemotherapeutic agents (Figure 1).

When a drug is infused into an extravascular cavity, the steady-state concentration in the cavity and plasma is a function of the *rate of clearance* from the cavity and plasma. For drugs that demonstrate *low* clearance from the cavity and *high systemic* clearance, there will be a pharmacokinetic advantage for the cavity into which the drug has been instilled compared with the systemic circulation.[1] Important determinants of clearance include the molecular weight of the drug, its charge, lipid solubility and the volume of fluid in which the drug is administered.[11] A drug with a low clearance from a body cavity would be one that has a high molecular weight, is ionized and water soluble and is administered in a large treatment volume.

A second important issue relates to the metabolism of the administered drug. Molecules the size of chemotherapeutic agents are principally taken up in the portal circulation when instilled in the peritoneal cavity.[12-14] Thus, a drug administered intraperitoneally that is hepatically metabolized might show a major pharmacokinetic advantage when administered by this route if it can be converted into a nontoxic metabolite before entering the systemic circulation.

A third principle for the successful application of intracavitary chemotherapy is the importance of treatment volume.[15-17] When drugs are delivered for their sclerosing properties, high concentrations are administered in small volumes. To prevent sclerosis and insure adequate exposure of drug to all tumor in the cavity, it is important to deliver the treatment in *large* volumes. In animals[18] and in several clinical trials,[19,20] the importance of treatment volume in overcoming the problems of drug distribution during intraperitoneal chemotherapy has been convincingly shown. This is a particularly important issue in many patients with intra-abdominal malignant lesions, as extensive adhesion formation induced by a prior surgical procedure or the tumor itself can possibly prevent access of drug to the entire abdominal cavity.

An additional question concerning the applicability of intracavitary chemotherapy is that of drug penetration. Little is known about the ability of most chemotherapeutic agents to penetrate into solid tumors.[21,22] Because of its intrinsic fluorescence, Ozols and co-workers were able to examine the penetrability of doxorubicin in a transplantable murine ovarian teratoma.[23] Whereas doxorubicin was found in only the outermost five to six cell layers of tumor when administered by the intraperitoneal route, this form of treatment was successful in curing 70% of the mice treated. When mice with this tumor were similarly treated with a regimen of intravenously administered doxorubicin, there were no long-term survivors.[24]

Theoretically, the intracavitary form of therapy will be most effective against free-floating tumor cells or thin tumor nodules. Free surface diffusion is unlikely to kill a large fraction of tumor in cases of advanced disease where large tumor masses are present. However, if drugs are used at or near their

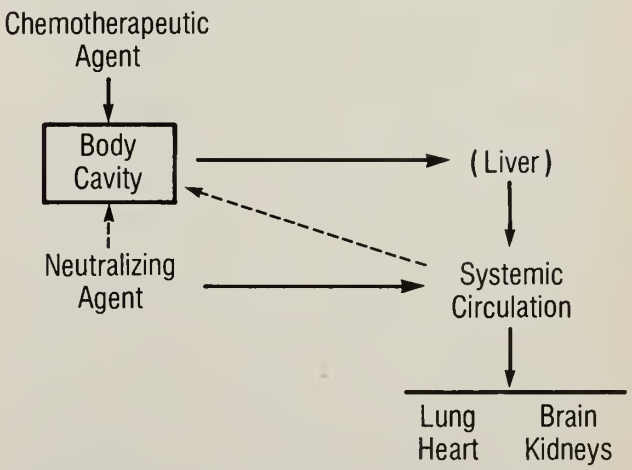

Figure 1.—Diagrammatic presentation of the basic principles of intracavitary chemotherapy. A drug administered via the intracavitary route will be absorbed into the systemic circulation at a rate determined by its physical and chemical characteristics. Drugs administered intraperitoneally can be metabolized in the liver into a nontoxic form before entering the systemic circulation. Finally, this treatment approach allows for the use of systemically delivered neutralizing agents to further enhance the pharmacokinetic advantage (see text).

maximum tolerated doses, then the combination of drug delivery by capillary flow (from drug absorbed into the systemic circulation) and free surface diffusion may still be more effective than intravenous dosing alone.

Finally, the large concentration differences achieved between the body cavity and plasma present the opportunity to make use of neutralizing agents delivered into the systemic circulation to reduce toxicity, while allowing high levels of drug to be present in the cavity treated. Two examples of this technique that have been clinically useful are the use of systemically delivered folinic acid[25,26] and sodium thiosulfate[20,27] administered to neutralize the toxicities of methotrexate and cisplatin, respectively. Results of clinical trials using these two neutralizing agents will be discussed in the following section.

Mention should also be made of the practical difficulties associated with intracavitary chemotherapy. Drug escaping from the body cavity can cause systemic side effects. In fact, if no local toxic reaction is encountered, dose-limiting toxicity will be similar to that seen when the agent is administered systemically. However, certain drugs might be quite irritating to the serosal surfaces and lead to pain and fever (chemical peritonitis or pleuritis), which must be distinguished from infectious causes. In addition, inflammation induced by the chemotherapeutic agent might result in adhesion formation, which can interfere with drug distribution and lead to bowel obstruction or loss of pulmonary function.

The delivery of drugs into body cavities requires a safe delivery system. Patients with a large volume of ascites or pleural effusions can be treated by the percutaneous placement of catheters specifically used to deliver the treatment. However, patients without such fluid or those responding to therapy with a decrease in malignant effusions require the surgical placement of semipermanent indwelling catheters to administer the treatment volume. There is significant experience in the safe use of such systems in patients requiring peritoneal dialysis, and similar devices have been adapted for use in patients being treated with intracavitary chemotherapy. Unfortunately, with indwelling catheters there is the risk of contamination of the system with the administration of therapy or with manipulation to drain fluid or inject heparin.

Single-Agent Intracavitary Chemotherapy

5-Fluorouracil has been evaluated for its safety and utility when administered by the intraperitoneal route.[14,28,29] In a clinical trial conducted at the National Cancer Institute (NCI), ten patients with refractory malignant tumors were treated with concentrations of 5-fluorouracil from 5 μmol to 8 mmol per liter (1.3 to 2,080 mg) in two liters of fluid. Dose-limiting toxic effects included pancytopenia and mucositis at concentrations of 4.5 mmol per liter. Abdominal pain was also significant and bacterial peritonitis developed in several patients. Objective antitumor responses were observed in several patients with ovarian carcinoma for whom standard chemotherapy given intravenously had previously failed.[28,29] A major pharmacokinetic advantage for peritoneal cavity drug exposure was shown (Table 1). In a second study, the NCI investigators found that total drug delivery of 5-fluorouracil to the liver via the portal circulation following intraperitoneal therapy was comparable with that achieved following direct intra-arterial drug administration.[14] However, additional trials will need to be conducted to define the safety and efficacy of the intraperitoneal approach to the treatment of metastatic disease in the liver. This is particularly important as it is known that 95% of the blood supply to a large metastatic lesion in the liver comes from the hepatic artery, with only 5% being delivered via the portal circulation.[34]

TABLE 1.—*Pharmacokinetic Advantage of Intraperitoneal Drug Administration*

Drug	*Mean Peak Peritoneal/Plasma Concentration Ratio*	*Sources*
Cytarabine	664	King and Howell[30]
5-Fluorouracil	298	Speyer et al[14,28]
Methotrexate	92	Howell et al[26]
Doxorubicin hydrochloride	474	Ozols et al[31]
Melphalan	93	Pfeifle et al[32]
Cisplatin	20	Howell et al[20]
Mitomycin	71	Adams et al[33]

As previously mentioned, the intracavitary administration of methotrexate allowed one to examine the utility of a systemically administered neutralizing agent. Investigators at the NCI delivered increasing dosages of methotrexate intracavitarily, with folinic acid rescue administered as a continuous infusion from 40 to 56 hours after the initiation of the methotrexate infusion.[25] While no definite clinical activity was shown in this trial, toxic reaction was mild and a significant pharmacokinetic advantage for peritoneal cavity drug exposure was found (Table 1). In a trial conducted at the UCSD Cancer Center, folinic acid was administered systemically simultaneously with the intracavitary delivery of methotrexate.[26] Toxic effects included mild abdominal pain and myelosuppression. Responses were observed in several patients with advanced refractory malignant tumors. These two clinical trials show contrasting approaches to the use of neutralizing agents. In the NCI trial the folinic acid was administered as a *rescue* agent following intracavitary drug delivery. In the UCSD trial the two drugs were given simultaneously. This allows for longer exposure of the body cavity to the cytotoxic agent, a major possible therapeutic advantage for a cell-cycle phase-specific agent such as methotrexate. Unfortunately, this latter technique runs the risk of neutralizing the methotrexate by the diffusion of folinic acid from the systemic circulation into the treated cavity (Figure 1).

The intraperitoneal administration of doxorubicin has been examined at the NCI.[31] Ten patients with refractory ovarian carcinoma were treated with doxorubicin at from 10 to 50 mg (9 to 54 μmol) in a two-liter treatment volume. None of the patients had previously received doxorubicin. There were five clinical responses including objective evidence of tumor regression in three patients and decrease in ascites in two additional patients. A dose-limiting toxic effect was abdominal pain at greater than 40 mg (36 μmol) in the two-liter volume. However, in spite of local toxic reaction limiting the dose of doxorubicin that could be administered intraperitoneally, a significant pharmacokinetic advantage for this route of drug delivery was shown (Table 1).

The safety and efficacy of the intracavitary delivery of cisplatin, one of the most active chemotherapeutic agents in ovarian carcinoma,[35] have been examined by several investigators.[20,36,37] As previously discussed, the simultaneous intravenous delivery of sodium thiosulfate administered to pre-

vent renal insufficiency caused by cisplatin has allowed the dose of this agent to be significantly escalated. Thiosulfate, an agent used clinically in high doses in humans for cyanide poisoning, had previously been found in mice to significantly protect against the nephrotoxicity of cisplatin.[38] This agent presumably combines with and inactivates the reactive site on cisplatin, neutralizing both its toxic and antitumor effects.

In a clinical trial conducted at the UCSD Cancer Center, cisplatin was able to be administered at a dose of 270 mg per m^2 (compared with the maximum intravenous dose of 120 mg per m^2) with minimal nephrotoxicity.[20] The cisplatin was administered in a volume of two liters with a four-hour dwell, after which any remaining fluid was removed. Only 7% of the instilled cisplatin could be recovered at the end of the four-hour dwell period. Myelosuppression was mild in this trial but cisplatin-induced emesis was substantial. The peak peritoneal concentration of free reactive cisplatin averaged 21-fold higher than plasma levels and the area under the concentration elimination curve averaged 12-fold more than under the plasma curve. What was perhaps most interesting, however, was that the area under the concentration curve for the plasma (at a dose of 270 mg per m^2) *increased* twofold compared with that for cisplatin administered intravenously at a dose of 100 mg per m^2. It is our hypothesis that whereas sodium thiosulfate does neutralize cisplatin, this reaction is slow at the concentration of thiosulfate in the plasma, but proceeds rapidly and completely in the kidney where the thiosulfate is concentrated.[39] Objective responses were shown in a number of patients with advanced intra-abdominal malignant lesions treated on this trial.

As unexpected activity of the intracavitary administration of cisplatin was found in several patients with malignant mesothelioma—a tumor that remains localized to the pleural or peritoneal cavities for much of its natural history[40]—a trial of this form of therapy has been conducted at our center to better define its efficacy.[41] A response rate of about 50% has been observed that is equal to that reported with intravenous administration of doxorubicin, the most active agent in this disease.[42] Cisplatin administered intravenously has a reported response rate of only 10% in cases of malignant mesothelioma.[42]

Melphalan has also been examined for intraperitoneal drug administration.[32,43] Whereas a pharmacokinetic advantage has been shown for the drug administered by this route (Table 1) with acceptable local toxic effect, there has been little clinical activity shown in patients with refractory tumors. However, with the demonstrated ability of this agent to achieve both high local and systemic concentrations when administered intraperitoneally, a strong argument can be made that this is the most rational method by which to deliver this agent to patients who have ovarian carcinoma.[32]

Investigators have evaluated the intraperitoneal delivery of mitomycin to patients who have advanced intra-abdominal tumors.[33,44] Whereas increased peritoneal cavity exposure to this drug has occurred compared with the plasma and clinical responses that have been noted, in several patients treated with this agent a chemical peritonitis developed.

Cytarabine was predicted on the basis of modeling studies to have a major pharmacokinetic advantage when administered intraperitoneally.[1] This agent is rapidly inactivated by deamination in the liver,[45] and, as previously mentioned, the absorption of compounds delivered intraperitoneally is principally through the portal circulation.[13] In addition to confirming the modeling predictions (Table 1), in a recent clinical trial both the safety and efficacy of the intraperitoneal administration of cytarabine in cases of ovarian cancer have been shown.[30] Ten patients with refractory ovarian carcinoma were treated with 60 μmol cytarabine (30 mg in a two-liter treatment volume) every six hours by dialysis exchange for five days. Treatment was repeated every 28 days. Two patients had complete clinical remissions that have persisted for longer than one year. Systemic side effects, principally myelosuppression, were mild and there was no local toxic reaction noted. Unfortunately, several episodes of bacterial peritonitis developed during the 20 courses of cytarabine administered during this trial.

Combination Intracavitary Chemotherapy

The superiority of combination chemotherapy over the administration of single agents in treating malignant disease has a sound theoretic basis (decreased emergence of resistant cells)[46,47] and has been confirmed clinically. In cases of several different types of tumors, combination therapy has been successful in producing complete responses whereas the use of single agents has resulted in only partial remissions. A second possible advantage for the administration of a combination of drugs during intracavitary chemotherapy is the potential for antitumor synergy among the agents used. For example, pronounced synergy has been shown in vitro between cisplatin and cytarabine against Lovo cells (a transplantable colon cancer cell line).[48-50] With the highest dose of cytarabine tested, a remarkable 1,600-fold increased cell kill occurred with this treatment combination compared with the use of cisplatin alone.

In a recently completed clinical trial at the UCSD Cancer Center, 31 patients with advanced intra-abdominal malignant tumors were treated with a combination of cisplatin, cytarabine and doxorubicin.[51] The toxic effects were acceptable except for doxorubicin-induced local abdominal pain. Responses, including considerable decreases in ascites and conversion of positive peritoneal cytologies to negative, occurred in 7 of 15 patients with ovarian carcinoma for whom intravenous chemotherapy regimens, including cisplatin, had previously failed. In a second trial, the dose of cytarabine was increased to take further advantage of possible concentration-dependent synergy betwen cisplatin and cytarabine. Doxorubicin was dropped from the treatment regimen to reduce local toxic effects. About 40% of patients with refractory ovarian carcinoma had objective responses to this program with significantly less abdominal pain compared with the previously mentioned three-drug combination.[52]

Combination intracavitary chemotherapy has also been effective in treating malignant pleural disease. Patients treated with either cisplatin, cytarabine and doxorubicin or cisplatin and cytarabine have shown dramatic decreases in the rate of reaccumulation of pleural fluid.[53] For several reasons it is believed the responses in patients treated with these treatment combinations are not due solely to the induction of sclerosis. First, none of the patients treated had local pain, a common and often severe complication of sclerosing therapy. Second, chest tube drainage was not used as part of the treatment program, an important component of most sclerosing treat-

ment regimens. Finally, several responses were observed in patients ten days to two weeks after therapy was administered, with patients initially showing rapid reaccumulation of fluid. This would suggest that the drugs are not acting directly on the pleural surfaces but rather on the tumor cells themselves, and it is only when the tumor has been killed and removed that a decrease in fluid reaccumulation will occur.

Conclusion

The field of intracavitary chemotherapy is in its infancy. Much work remains to be done to define optimal drug combinations and schedules for the various tumors to be treated by this route of drug administration. In addition, improved methods of delivery must be developed to assure adequate drug distribution and reduce the risk of chemical irritation and bacterial infection. Finally, it will eventually be necessary to show in controlled clinical trials whether the pharmacokinetic advantage of intracavitary drug administration can be translated into improved response rates and survival.

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Specialty Conference

Photochemical Air Pollution
Part I

Moderator
ELLIOT GOLDSTEIN, MD

Discussants
ELLIOT GOLDSTEIN, MD; JACK D. HACKNEY, MD, *and* STANLEY N. ROKAW, MD

An edited transcription of an Interdepartmental Conference arranged by the Department of Medicine of the University of California, Davis, School of Medicine.

ELLIOT GOLDSTEIN, MD:* The levels at which air quality standards for photochemical oxidants, specifically ozone and nitrogen dioxide, are set have enormous health and economic consequences for the American public. Estimates of the danger from photochemical pollution suggest that these pollutants contribute to some deaths and to numerous illnesses each year.[1-3] Although the validity of these estimates that compare pollution with crude morbidity and mortality figures is uncertain, the fact that by-products of industrial and transportation processes are blamed for widespread illness has resulted in political and economic as well as scientific considerations entering into their control. Governmental and scientific experts who subscribe to the above assessment of photochemical risk advocate maintaining established air quality standards and, where necessary, instituting stricter standards to ensure full protection of the public health.[4,5] Thus, these experts believe the billions of dollars required of industry to reduce air pollution[6,7] are justified despite the lack of definitive proof validating present standards.[8]

In contrast, as a result of the energy shortage, other members of the governmental and scientific communities have reconsidered the present standards and concluded that they are unduly restrictive.[9-11] In their view, lower air quality standards will adequately protect public health and welfare. If these experts who contend that more lenient standards will not endanger the public health are right and the health hazard is overestimated, billions are being spent unnecessarily. The extent to which each viewpoint is correct is of crucial importance in these years in which air-quality regulations are being reviewed. The goal of this conference is to evaluate the available scientific evidence pertaining to human health effects in a manner permitting reasoned decisions for controlling air pollution. Damages to agriculture and materials, which are additional consequences of photochemical oxidant pollution, are not discussed in this conference; the interested reader is referred to detailed reports on those subjects.[12,13]

Sources and Fate of Atmospheric Nitrogen Dioxide and Ozone

Nitrogen dioxide (NO_2) enters the atmosphere as a by-product of combustion processes in which temperatures are high enough to fix atmospheric nitrogen. In the United States, fuel combustion in gasoline engines and in power production and other industrial processes are the primary sources, each contributing approximately 11 million metric tons per year of nitrogen oxides.[14] Through a series of complex photochemical reactions, NO_2 and hydrocarbons, which are also produced during combustion, convert oxygen to ozone.[15] As a result, the mean daily maximum ozone concentration for the high-pollution period of May to October ranges from 0.07 ppm in less polluted areas of California to 0.14 ppm in the heavily polluted areas surrounding Riverside, California.[16] Corresponding mean daily maximum hourly concentrations of NO_2 are 0.05 ppm and 0.1 ppm.[16]

Because of differences in physical properties, the fate and distribution of ozone and nitrogen dioxide differ following inhalation. Ozone is a soluble and highly reactive gas that, according to theoretical models of absorbance, affects primarily cells of the upper airways and respiratory bronchioles; significantly smaller amounts reach alveoli and extrapulmonary sites.[17] At these sites, ozone damages tissues by rapidly oxidizing unsaturated fatty acids and thiol-containing compounds.[18] In contrast, studies with nitrogen dioxide N 13 show that this less reactive gas is distributed more evenly

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ABBREVIATIONS USED IN TEXT

FEV_1 = forced expiratory volume in one second
FVC = forced vital capacity
NO_2 = nitrogen dioxide

throughout the lung and disseminates to extrapulmonary sites (Figure 1).[19] Chemically, nitrogen dioxide reacts with water to form nitrous and nitric acid, the compounds responsible for cellular toxicity.[19,20] Nitrous acid also reacts with amines to form potentially carcinogenic nitrosamines.[21] The extent to which these injuries occur for differing photochemical oxidant exposures has been studied in volunteers, in epidemiologic surveys and in animal investigation. In the following sections we discuss results obtained from these studies and their relationship to present air-quality standards of 0.12 ppm of photochemical oxidant for one hour[22] and 0.05 ppm of NO_2 for the annual mean concentration.[23]

Controlled Studies of Volunteers Exposed to Ozone and Other Photochemical Oxidants

JACK D. HACKNEY, MD:* Scientific research used to establish environmental protection laws must be judged by rigorous criteria that ensure reliability and applicability. Direct evidence in humans should meet criteria of scientific rigor (normal peer review and journal publication), redundancy (independent confirmation by a second peer-reviewed study) and relevance to public health (similarity of the experiment to real pollution exposures in terms of the people studied and the pollutant concentrations to which they are exposed). When these conditions are satisfied, the chances of either inadequate or excessive regulatory response to pollution problems are minimized.[24] This caveat should be kept in mind when considering some of the experimental results discussed in this presentation, which are preliminary and have not as yet satisfied the criteria.

Laboratory studies of volunteers exposed to photochemical oxidants under controlled conditions provide the most data about the short-term effects of these pollutants. In these studies, healthy subjects and persons with chronic lung disease have been exposed from one to several hours to ozone at concentrations relevant to ambient levels, and symptoms and changes in pulmonary physiology are recorded. These studies have generated information to answer the following questions: What measure of pollutant exposure produces measurable responses, and what factors alter responsiveness?

During the 1970s, in most controlled studies of ozone, light to moderate intermittent exercise was used, simulating typical outdoor activity for most people. Usually, under these conditions, no abnormalities in respiratory function were found after exposure for one to two hours to ozone concentrations near 0.2 ppm.[25,26] Similar exposures to concentrations of 0.3 ppm and higher resulted in symptoms of respiratory irritation and reduction in forced expiratory volumes. At these levels, the subjects had cough, dyspnea, throat and chest soreness and deficits in respiratory function attributed to increases in airway resistance, diminished lung elasticity or obstruction of small airways.[27-33] The severity of the symptoms and respiratory dysfunction paralleled the intensity of exposure. Figure 2 shows an exposure/response depicting this relationship.[34] Such effects are transitory, lasting a few hours at most.

Persons living in smoggy environments often carry on strenuous activities or are exposed repeatedly to high ambient levels of ozone. Both conditions have been simulated in a laboratory by having volunteers exercise heavily while exposing them to ozone or by exposing them for one or more hours on consecutive days (or a combination of these). Two of six volunteer men who exercised strenuously (up to 65% of their maximum oxygen uptake) for one hour while breathing 0.15 ppm of ozone had modest decreases in forced expiratory function; neither was able to complete an hour of similarly strenuous exercise when exposed to 0.3 ppm of ozone.[35] Re-

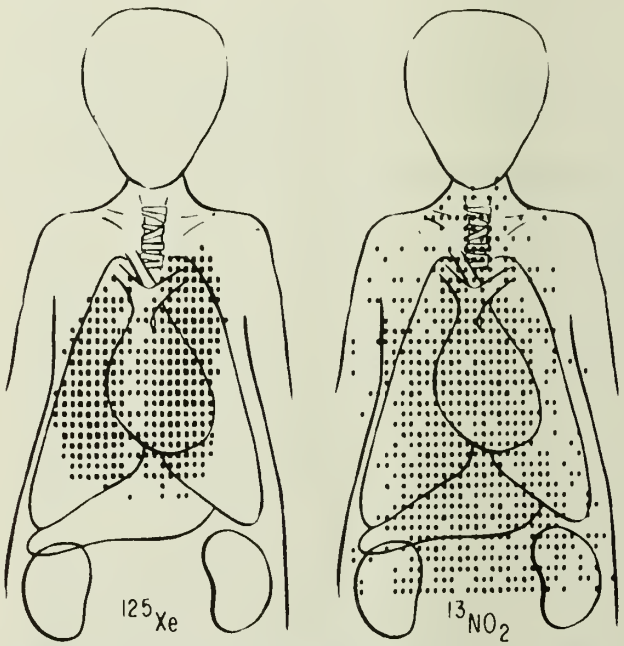

Figure 1.—Pulmonary radioactivity patterns following inhalation of xenon Xe 125 (^{125}Xe) and nitrogen dioxide N 13 ($^{13}NO_2$) in a rhesus monkey showing confinement of the insoluble ^{125}Xe to the lung and extrapulmonary dissemination of the more soluble $^{13}NO_2$. (Modified from Goldstein et al.[19])

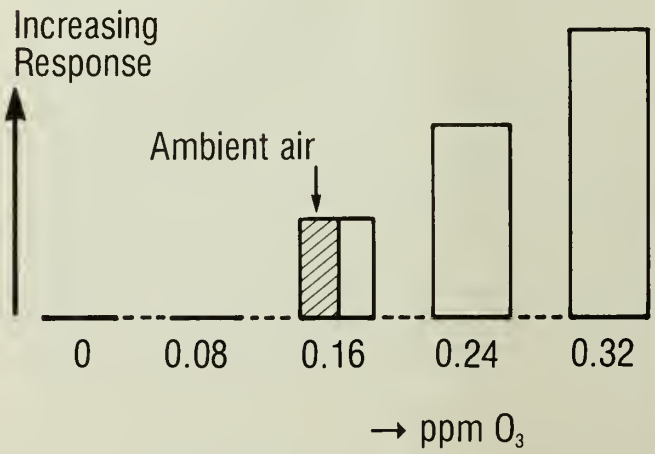

Figure 2.—Schematic representation of exposure-response behavior in ozone or ambient oxidants under heavy exercise. Response measured as symptoms or forced expiratory function decrement. Bars of different height represent significant ($P<.05$) differences in response. Ambient-air ozone (O_3) concentration range, 0.12 to 0.19 ppm.

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cently, independent studies have confirmed these findings of respiratory irritation in strenuously exercising persons breathing less than 0.3 ppm of ozone.[34,36] It is worth emphasizing that one- to two-hour exposures to 0.2 ppm of ozone occur frequently in Los Angeles and occasionally elsewhere. At high concentrations (0.6 ppm) ozone provokes exaggerated bronchial responses to histamine that can be prevented by pretreatment with atropine, indicating that at these concentrations pollutant-induced bronchial hyperreactivity involves cholinergic pathways.[37]

In contrast to heavy exercise, which increases susceptibility to ozone-induced respiratory abnormalities, repetitive daily exposures do not progressively enhance vulnerability. Volunteers exposed for two hours per day to 0.5 ppm of ozone for four successive days typically have enhanced effects on day two and diminished responses thereafter.[38,39] This "adaptive" response, found in most but not all subjects, is lost within a few days after the last exposure.[40] Because the capacity to "adapt" to ozone is transient, relying on adaptation for protection against ozone is unwarranted.

Patients with bronchial asthma or atopic subjects sometimes appear to be more sensitive to inhaled irritants than persons without a history of respiratory illness. However, increased sensitivity to ozone of persons with asthma is not firmly established, and the issue needs more investigation.[41,42] If the sensitivity of asthmatic persons is higher, it is so only to a slight degree. Likewise, patients with chronic obstructive lung disease are often assumed to be more sensitive to ozone than healthy persons. Several controlled experiments exposing volunteers who have chronic obstructive lung disease have shown that these presumably high-risk persons have about the same sensitivity to ozone as do healthy persons; in both groups, physiologic changes of questionable clinical significance (slight increases in airway resistance and oxygen desaturation) first appear after a two-hour exposure to 0.3 ppm.[43–46] Inability to increase ventilation with exercise may play an important role in limiting the ozone exposure of patients with chronic obstructive lung disease during experimental studies. Because sensitivity to ozone varies considerably among persons and because few people have been studied, hypersensitive patients with pulmonary disease who react to high ambient levels of ozone may still be found, but as yet, the presence of supersensitive persons is unproved.

Sensory perception of odor is a sensitive indicator of the presence of nitrogen dioxide as well as ozone. When healthy volunteers are exposed to NO_2, some perceive the odor at 0.12 ppm and most detect it at 0.42 ppm.[47] Concentrations of NO_2 must be higher to produce respiratory dysfunction. For example, increases in airway resistance, a sensitive physiologic indicator of dysfunction, are reported following two-hour exposures of resting subjects to NO_2 levels of 2.5 ppm; higher concentrations did not result in progressive dysfunction.[48] When data from several laboratories are pooled, however, the same dose-effect relationship noted for ozone occurs with NO_2: increasing concentrations produce increasing respiratory dysfunction.[49] Several controlled exposure studies, with protocols involving light to moderate exercise, have been done with NO_2 at concentrations attainable in severe ambient pollution episodes—0.5 to 1.0 ppm. Effects on respiratory mechanics and symptoms were small and equivocal at best.[50–52] In contrast to ozone, NO_2 is unlikely to be of concern in athletic competitions in smoggy areas.

Pulmonary airways of patients with chronic bronchitis are slightly more sensitive to the irritative effects of NO_2; a 15-minute exposure to 1.6 ppm NO_2 increased the airway resistance in one such group.[53,54] However, as these levels are much above ambient and because lower NO_2 concentrations do not produce abnormalities, short-term exposure to ambient levels of NO_2 is unlikely to increase airway resistance in patients with chronic bronchitis.

One provocative finding was reported by Orehek and coworkers, who tested the effect of a one-hour exposure to very low levels of NO_2 (0.1 and 0.2 ppm) on airway resistance in 20 asthmatic patients before they inhaled increasing doses of the cholinergic drug carbachol.[55] After a preexposure carbachol dose-response curve was recorded, the subjects were exposed to NO_2, and carbachol was readministered to determine whether the pollutant changed the subjects' bronchial sensitivity to the agent. Bronchial reactivity increased in 13 of 20 subjects when comparisons were made between the NO_2 and clean air exposures. Thus, if one assumed that the cholinergic aerosol simulated an environmentally occurring bronchoconstrictive agent, NO_2 exposure enhanced the vulnerability of asthmatic persons to bronchoconstriction. Because patients did not have symptoms despite potentiation of bronchial reactivity and because the higher concentration of NO_2 (0.2 ppm) did not further potentiate the bronchoconstrictive effect, the significance of these studies was contested and they were repeated in other laboratories.[56–58]

Our laboratory conducted one of the reinvestigations of the effect of NO_2 on bronchial reactivity consequent to bronchoconstrictor inhalation. Our results were equivocal with respect to the NO_2 effect.[56] A small mean increase in bronchial reactivity occurred, which was significant in some but not all statistical tests comparing the NO_2 and clean air exposures. A preliminary report of another recent study indicates similarly equivocal results.[57]

In a third recent study essentially no effect was found.[58] Thus, at present, the conclusion that low levels of NO_2 definitely potentiate bronchoconstriction in asthmatic patients is unproved. Even if potentiation occurs, its clinical significance is uncertain.

The aforementioned studies tested ozone or NO_2 alone. Because polluted air contains a variety of gaseous and particulate pollutants, realistic assessments of photochemical-oxidant-polluted air require data from studies in which volunteers are exposed either to actual ambient air during periods of high pollution or to complex artificial atmospheres that simulate ambient conditions. We have emphasized the former approach in studies using a unique movable laboratory.[59] In a recent study competition bicyclists continuously bicycled for one hour while exposed to purified air containing 0, 0.08, 0.16, 0.24 and 0.32 ppm of ozone and to oxidant-polluted air in suburban Los Angeles (mean minute volume, 55 liters). Exposures occurred in random order two weeks apart. Symptoms and forced expired volume in one second (FEV_1) were recorded preexposure and postexposure. Ozone levels in ambient exposures averaged 0.15 ppm and ranged from 0.12 to 0.19 ppm. Mean levels of total particulates, nitrates and sulfates were 281, 39 and 13 mg per m^3, respectively. Mean FEV_1 loss in ambient air was similar to that that occurred in purified air containing 0.16 ppm of ozone (Figure 2). These losses were modest but statistically significant. More severe losses occurred with 0.24 and 0.32 ppm of ozone. The symp-

toms paralleled the FEV_1 responses. Thus, this well-conditioned, heavily exercising population of bicyclists manifested impaired respiratory function and symptoms of pollutant irritation when exposed to moderately polluted Los Angeles atmospheres. These effects could be attributed to ozone alone because much the same effects occurred in persons exposed to similar levels of ozone without other pollutants. Similar results have been reported in lightly exercising volunteers.[29,30]

The addition of 0.3 ppm of NO_2 did not elicit symptoms or produce respiratory dysfunction in persons exposed to 0.25 ppm of ozone—a subthreshold dose in this experiment[30]—nor did it augment symptoms and dysfunction in reactive persons exposed to 0.5 ppm of ozone.[29]

In summary, volunteer studies have clearly shown ventilatory disturbances in light to moderately exercising healthy persons exposed to 0.3 ppm of ozone, a level that occurs, albeit infrequently, in polluted areas. Lower levels of oxidant approximating the air-quality standard of 0.12 ppm for one hour have not provoked ventilatory dysfunction in lightly exercising healthy persons or in patients with chronic obstructive pulmonary disease or bronchial asthma; the latter persons apparently have sensitivity to ozone similar to that of normal persons. Exercise increases vulnerability to oxidant-induced ventilatory dysfunction, and some highly trained athletes manifest small but significant impairments in pulmonary function as well as irritative symptom complexes when exercised strenuously for one hour while breathing 0.15 ppm of ozone. Last, exposure to NO_2 at concentrations at least three times higher than ambient maxima do not produce ventilatory disturbances in healthy persons or patients with chronic bronchitis and it is uncertain whether low levels of NO_2 potentiate bronchoconstriction in asthmatic patients.

Epidemiologic Studies of Health Effects of Oxidant Pollutants

STANLEY N. ROKAW, MD:* Because ethical considerations preclude inducing illness in volunteers, epidemiologic studies are a principal pathway to determining the hazards of ambient concentrations of photochemical oxidants. Such studies, however, are exceedingly difficult to accomplish because (1) it is virtually impossible to maintain and study populations similar in all characteristics except pollution exposure; (2) confounding variables such as temperature, cigarette smoking, preexisting disease and subject compliance hinder acquiring enough information to detect subtle differences due to air pollutants and (3) uncertainties often exist in regard to actual exposures of persons in the study group. Despite these formidable difficulties, a number of epidemiologic investigations have been done. These will be reviewed in a "4-D" system: relationship to death, disease, dysfunction and discomfort.

Studies comparing the mortality of exposure to photochemical oxidants have failed to prove a relationship between these oxidants and deaths due to lung cancer,[60] respiratory failure[61-63] or any other cause.[64] Deaths were associated with exposure to elevated levels of photochemical oxidant in two studies, but because mortality coincided more closely with concomitant elevations in temperature, the actual effect of the oxidants is uncertain.[61,63,64] Although ozone itself does not influence mortality, the association of temperature and photochemical oxidant exposure with mortality suggests the possibility of an additive interaction.[61,64,65] Such interaction, however, is unproved and presents a potentially fruitful area for future research.

The available epidemiologic data also indicate that serious illness is not directly caused by photochemical oxidant exposure. Exacerbations of asthma and nonspecific obstructive respiratory disease are the illnesses most often linked to oxidant exposure. Studies comparing incidences of asthmatic attacks with oxidant levels in the Los Angeles area have yielded suggestive but inconclusive evidence associating the two phenomena.[65-68] In two studies in which weekly questionnaires were used, small correlations were found that suggested that subgroups of asthmatic persons were sensitive to elevated levels of oxidant.[66,67] However, because ascertainment of the attacks was based on nonclinically validated subjective appraisals and because other factors like temperature also correlated with increases in attack rates, the importance of the association of asthma and pollutant exposure is uncertain. Similar results were obtained when parents of asthmatic children were questioned about symptoms during two air-pollution alerts in Los Angeles in which oxidant levels reached 0.19 ppm or higher.[68] According to the parents, the children's asthma and nasal allergies worsened and eye irritation developed. Because the average number of emergency room visits for asthma decreased during this period, either the incidence of severe attacks did not increase in the general population or people were sufficiently educated to stay indoors during alerts and to not come to emergency rooms unless the attack was unusually severe. Twelve patients with very severe asthma at a home for asthmatic children did not have increased symptoms or excess need for medication during the high pollution periods, although they did have decreased performance on pulmonary function testing.[68] One explanation for these dichotomous results is that only a subgroup of persons with asthma are hypersensitive to pollutants and this subgroup was obscured in the statistical analysis of the larger group.

Studies comparing nonasthmatic respiratory illness, dysfunction and discomfort with exposure to photochemical oxidants[69-86] and nitrogen dioxide[87-105] have also shown only modest increases in manifestations of illness when ambient levels are excessively high. Exposure to ambient levels of 0.15 ppm of oxidant provokes cough and throat and chest irritation in young, healthy adults.[69,70] Whether these symptoms by themselves are classified as disease or discomfort depends on one's definition of disease. If disease is defined as "any deviation from or interruption of the normal structure or function of any part, organ or system of the body,"[106] then these studies prove that exposure to high ambient levels of photochemical oxidants produces mild, self-limiting respiratory disease. Because diagnostic tests were not done in these epidemiologic studies, the cause of the respiratory disease is unknown. The transient nature of the disease and the lack of fever suggest an irritative rather than a bacterial or viral origin. Similar respiratory symptoms do not occur in most healthy persons exposed to lesser concentrations of photochemical oxidants[71,72] unless they have predisposing factors, like a history of smoking or respiratory illness.[73]

Photochemical oxidant exposures do not render persons more susceptible to influenza or increase their extent of illness. Two retrospective studies have been done in southern

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California and in Sofia, Bulgaria, following influenza epidemics in which air pollution exposure was correlated with the occurrence and severity of influenza.[74,75] Neither the California study, in which a questionnaire was used, nor the Bulgarian study, in which absentee records were analyzed, showed an association.

Several studies have been done to determine whether oxidant exposures aggravate chronic bronchitis or emphysema. Findings in the early studies suggested that pulmonary function could improve when patients with emphysema were placed in rooms from which oxidants were removed with filters.[76,77] The validity of these conclusions, however, is in doubt because variations in smoking habits, which would influence the results, were not included in the study designs.[65]

In more recent studies Detels, Rokaw and colleagues have compared the effect of prolonged exposure to different levels of photochemical oxidants on pulmonary function of healthy persons with that of persons with chronic obstructive pulmonary disease.[78-81] These studies were carried out in several areas of Los Angeles. Comparisons are published for one area with high (Glendora) and one with low (Lancaster) oxidant levels in which the populations were similar in age, race, sex and socioeconomic status.[81] Air pollution was measured continuously at stations located in the midst of these populations. An interview questionnaire concerning smoking, occupation and occurrence of cough, sputum production, wheezing and chest illness was administered to all residents 7 years of age and older. All participants underwent spirometric, body plethysmographic and single-breath nitrogen washout and closing volume tests in a mobile pulmonary function laboratory whose equipment was cross-calibrated with similar equipment at the University of California, Los Angeles, Medical Center. A pronounced difference in air pollution exposure between the two communities was confirmed with annual mean values of 0.11 ppm of oxidant, 0.12 ppm of NO_2 and 13.5 mg per m^3 of sulfate particulates in Glendora and 0.06 ppm of oxidant, 0.03 ppm of NO_2 and 4.5 mg per m^3 of sulfate particulates in Lancaster during the years of the study.

In all, 96% (3,192) of households in Lancaster and 89% (2,369) of households in Glendora completed the questionnaire and testing. These results were analyzed separately for adults who never smoked, those who smoked one pack of cigarettes or less per day or those who smoked more than a pack per day. Symptoms, frequency of chest illness and impairments of respiratory function were significantly more common in smokers than in nonsmokers. The comparisons of smoking and nonsmoking persons in regard to residence showed that those living in Glendora had significantly more symptoms and lower pulmonary function values than did persons living in Lancaster (Table 1). These differences showing pollutant-associated increases in respiratory symptoms and decreases in respiratory function were independent of a number of possibly confounding variables—occupation, epidemics of intercurrent infection, prior respiratory illness, commuting patterns, migration and representativeness of monitoring data.

If confirmed, these cross-sectional studies showing an association between long-term exposure to high levels of photochemical oxidants and decreases in pulmonary function in smokers and nonsmokers are the most convincing evidence that ambient exposures to photochemical oxidants are harmful to health. Longitudinal studies are under way in these populations to determine whether the observed adverse pathophysiologic abnormalities are reproducible and whether they persist or accelerate in ensuing years.[80,81] Longitudinal studies require considerable investigator and economic commitment, and in these times of fluctuating academic and research support, whether or not they will be completed is uncertain.

TABLE 1.—*Degrees of Significance* for Differences in Symptom Prevalences and Lung Function Test Results for Persons From Lancaster and Glendora (California)†*

	Never Smoked	Currently Smoke	
		< 1 pack	> 1 pack
Symptom Prevalences			
Cough			
Men	.001	. . ‡	. . .
Women	.005	.05	. . .
Wheezing			
Men	.001	.001	.001
Women	.001	.005	.005
Sputum production			
Men	.05	. . .	. . .
Women	.05	. . .	.05
Tests			
FEV_1			
Men	.01	. . .	.001
Women	.001	.001	.001
V_{max} §			
Men	.001	.001	.001
Women	.001	.001	.001
Closing volume (4)			
Men	.001	.001	.001
Women	.001	.001	.001

FEV_1 = forced expiratory volume in one second, V_{max} = peak maximal expiratory flow rate

*Two sample positive tests were calculated. Probability values in these tests should be interpreted cautiously because sample sizes and rates may be too small to assume normality of the estimate.

†Modified from Detels et al.[81]

‡$P < .05$ not reported.

§Between mean values.

Dysfunction, usually of pulmonary systems but also involving the overall performance of exercising athletes, has been correlated frequently with ambient levels of oxidants. A recent study of school children at a summer camp in Pennsylvania correlated forced vital capacity (FVC) and FEV_1 diminution with oxidant levels of 0.12 ppm.[82] School children in Tucson had decreased ventilatory function after exercising in relation to oxidant levels, but these changes also correlated with temperature effects.[83] Track performance in Los Angeles was diminished when compared with expected performance values if the athletes were exposed to about 0.25 ppm of oxidants before the meet.[84] School children in Tokyo showed increased airway resistance and decreased maximum expiratory flow rates when oxidant levels were elevated. Lower airway impairment was also associated with concomitant nitrogen oxide levels. Some of these school children did not revert to "predicted" functional levels after the "smog" season.[85]

Discomfort manifested primarily as eye irritation has been noted in studies in California and Connecticut.[70,73] Student nurses in California, when tested prospectively about symptoms, consistently related headache, eye and chest discomfort and cough with exposure to oxidant levels above 0.15 and

0.19 ppm.[70] Panel members in Connecticut, particularly persons who were heavy smokers or had predisposing respiratory illnesses, reported increased eye irritation and coughing when exposed to higher levels of oxidants.[73]

Discomfort due to ozone has been a particular problem for the airline industry.[86] Ozone concentrations are about 1.0 ppm at 12,000 m (40,000 ft), and it has been known for years that passengers and crew members flying at high altitudes complain of chest pain, shortness of breath, coughing, wheezing and burning sensations in the throat and eyes. To overcome this problem, the Federal Aviation Administration limits ozone concentrations in airplanes to 0.1 ppm over a time-weighted average with a maximum of 0.25 ppm.[86]

Many epidemiologic investigators have attempted to correlate exposure to NO_2 with death, disease, dysfunction and discomfort.[87-105] It should be emphasized that although NO_2 is considered the principal pollutant in these studies, multiple pollutants were invariably present and the effects reported reflect exposure to combinations of pollutants including NO_2. Studies correlating mortality with exposure to NO_2 do not provide convincing evidence of an association.[87,88] Hickey and colleagues reported a positive correlation between mortality rates from various tumors and concentrations of NO_2 using a multiple-regression analysis for data obtained from 38 standard metropolitan statistical areas in the United States during the years 1961 through 1964.[87] A critique of this study indicates that although the statistical methods are appropriate, the data for pollutant concentrations and for mortality do not justify the statistical findings.[89] For example, neighborhood differences in pollutant exposure within the same standard metropolitan statistical area are often larger than the differences between areas, yet each area was treated as a single entity. In addition, the investigators collecting the mortality data consider the place of death to be the site of longest residence, an assumption that may be in error because of population mobility. An association between NO_2 exposure and mortality has not been noted in other studies[88] and in the absence of evidence proving that ambient levels of NO_2 are mutagenic, the association of mortality due to tumors with exposure to high ambient levels of NO_2 is unproved.

Epidemiologic studies correlating exposure to NO_2 with respiratory illness and dysfunction have yielded similarly inconclusive results. The air quality standard for NO_2 of 0.05 ppm on an average annual basis was established by the Environmental Protection Agency primarily as a result of an epidemiologic study in Chattanooga, Tennessee, that showed excess respiratory illness among families exposed to high ambient levels of NO_2 and reductions in ventilatory performance in children residing in these areas.[90-92] In these prospective studies, socially and economically matched communities were investigated that were exposed to high and low concentrations of NO_2 from a manufacturing plant producing trinitrotoluene (TNT). The average daily NO_2 concentration in the high-NO_2 area was 0.083 ppm, and the measurements followed were weekly ventilatory function tests, biweekly respiratory illness surveys and an assessment of susceptibility to influenza during an unexpected epidemic. According to the information obtained, families in the high-pollution areas suffered an excess number of acute respiratory illnesses; second-grade children were particularly affected during the influenza epidemic. Also, minor abnormalities in respiratory function were noted in the population exposed to the elevated levels of NO_2.[90] This study, which has been criticized on a number of accounts, points out the difficulties in epidemiologic investigations of air-pollutant effect. First, the Jacobs-Hochheiser method used to measure NO_2 was too imprecise.[9,93] Second, unmeasured amounts of sulfuric and nitric acid vapors and sulfate particulates were in the contaminating atmosphere.[94] Third, the statistically significant decrease in $FEV_{0.75}$, which formed the basis for the conclusion concerning respiratory dysfunction, was less than the precision of the test.[9] Although answers to some objections were provided,[8] enough uncertainty exists to preclude forming conclusions based on these studies.[89]

Other studies attributing increases in respiratory illness to exposure to high levels of NO_2 have been beset by similar problems.[95-98] Studies in Japan correlating increased rates of chronic bronchitis with exposure to elevated levels of air pollutants were done in populations exposed to elevated levels of suspended particulates as well as NO_2.[95] The same criticisms apply to studies from Russia and eastern Europe, in that populations incurring excesses of acute respiratory disease were exposed to high concentrations of sulfur dioxide, sulfuric acid and ammonia in addition to NO_2.[96-98] Evaluating the European studies is further complicated by incomplete documentation of the methods of measuring pollutants.

Recently, much controversy has been generated by a series of studies purporting to show that exposure to elevated levels of NO_2 from gas cooking stoves results in respiratory illness in childen.[99-105] Melia and colleagues assessed the occurrence of bronchitis, cough, chest colds, wheezing and asthma in thousands of children from randomly selected areas of England and Scotland over a four-year period, by means of a self-administered questionnaire.[99-102] The statistical analysis permitted adjustments for variables such as social class, pollution, population density, family size and overcrowding. Although the initial studies did not include measurements of NO_2 concentrations within homes, subsequent measurements showed that these concentrations varied between 0.005 and 0.317 ppm, with a mean value of 0.112 ppm, in kitchens with gas cookers and between 0.006 to 0.188 ppm, with a mean value of 0.018 ppm, in homes with electric ranges.[101] The results from the first year of the study showed a statistically significant association ($P=.05$) of symptoms of respiratory illness in girls from homes with gas cookers.[99] As the children grew older, the association persisted but became less significant, suggesting that the risk of NO_2-related respiratory illness declines with age.[100] Spirometric measurements in subsets of children from homes with high and low levels of NO_2 did not show differences, indicating that the high NO_2 exposure was not associated with physiologic dysfunction.[95]

In another study using recall questionnaires, significantly higher rates of respiratory illness were also shown in children from households with gas stoves.[103] Speizer and co-workers, in a study involving 8,120 children aged from 6 to 10 years living in six different American communities, noted an increased incidence of respiratory illness in children younger than 2 years.[103] From their study, which controlled for smoking, they also found significant, small reductions in FEV_1 and FVC in children living in homes with gas stoves compared with those living in homes with electric stoves. In contrast to these results, two prospective American studies,

one involving 1,952 persons, the other involving 586 persons and both evenly divided among households using gas and those using electric stoves, did not show differences in respiratory illness. These data were obtained from biweekly telephone calls[104,105] and in some cases by household visits to assess illness.[105] This lack of association applied for children younger than 12 and for their parents. Numerous variables, including smoking and previous illness, were controlled for, and monitoring in subsets of homes showed mean NO_2 concentrations of 0.05 ppm in homes with gas stoves and 0.02 ppm in homes with electric ranges. The NO_2 levels in these studies, which did not indicate enhanced susceptibility, were much below those found in the studies in England and Scotland.

In summary, findings from epidemiologic studies indicate that high photochemical oxidant exposures

- Do not cause mortality or serious illness.
- May increase the risk of asthmatic attacks in a small percentage of asthmatic patients.
- Appear to reduce pulmonary function in smokers and nonsmokers after long-term exposure.
- Cause acute discomfort of eye and throat, chest irritation and cough.
- Interfere with athletic performance.

Exposure to high ambient levels of NO_2 is not associated with mortality, serious disease or respiratory dysfunction, but self-limiting symptoms of respiratory irritation or illness may develop in children.

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Ozone and Photochemical Pollutants

Status After 25 Years

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Twenty-five years ago if one had stopped at a downtown Los Angeles traffic light while behind the wheel of a State of California Department of Public Health vehicle, it would not have been unusual for some irate citizen to come up to the window of the car and shout, "When are you going to get rid of the smog?" At that time there was substantial evidence of materials damage as manifested by rubber cracking experiments conducted at the California Institute of Technology and significant crop damage to the central valley cotton industry. On the basis of economic impact alone, something needed to be done to clean up the environment. In addition, there was no question, mainly because of eye irritation, that Los Angeles smog was a public annoyance, if not a proven health hazard. Strong leadership from the State Health Department has made California the leader in the nation for, first, identifying the problem and, second, developing abatement strategies to control photochemical pollution.

Over the years a substantial number of studies have been directed toward understanding the components and sources of the predominant pollutants and toward identifying potential health hazards. We have come to understand that ozone and nitrogen dioxide (NO_2) result from fossil fuel use from both stationary and mobile sources. Combined with relatively well-defined meteorologic factors, these pollutants result in photochemical pollution (smog) and are the major putative agents of concern. Furthermore, the level of sophistication of experimental procedures has improved remarkably.

An interdepartmental seminar held at the University of California at Davis has attempted to summarize the current state of knowledge. The results are both disappointing and encouraging. The specialty conference (which appears in two parts, part II to be published in a subsequent issue) brought together experts in veterinary pathology, experimental biology, physiology, epidemiology and economics to summarize the current state of knowledge and to recommend strategies to decide on appropriate safe levels of ambient exposure to ozone and NO_2. The discipline not represented at the seminar—and one that interacts with all the others—is that of air monitoring, both for measurements of regional pollutants and of exposure during short-term experimental studies.

Air monitoring is critical because none of the data on health effects can be used quantitatively unless estimates of exposure are available. Unfortunately, even under experimental conditions when exposure is being monitored, actual dose to the affected part of the airway or lung is still poorly estimated. Only the most sophisticated monitoring schemes that utilize radioactive-tagged substances, as discussed by Goldstein and co-workers,[1] give any real estimate of dose. It is, therefore, not surprising that as one moves from any true measure of dose to estimates of exposure in experimental settings or in population settings, misclassification of exposure becomes increasingly important and significantly handicaps the possible interpretations of the data.

The assessment of data related to the health effects of air pollutants is of concern to practicing physicians who must consider the data to make their own informed decisions and who must also define the issues for their patients. Since many physicians are called upon to express opinions on the subject, it is important for practicing physicians to understand how the various approaches to the study of air-pollutant health effects are being used to make important policy decisions.

Three kinds of studies—animal experimentation, controlled chamber exposure experiments in both animals and humans and population-based epidemiologic investigations—were discussed at the seminar. Each was summarized as to whether it proved a health effect for ozone or NO_2. Surely the importance of bringing the disciplines together was not to prove that one or the other answered the specific question about the potential health impact of these pollutants; no one area of investigation (as discussed below) can possibly provide all the information necessary to make a rational decision. Policy makers, we as practicing physicians and intelligent, informed citizens must utilize all of the available data taken together to reach decisions about dealing with any community-wide potential health impact.

Each of the approaches to the study of health effects provides insights that are all needed in the decision-making process. *Animal experimentation* allows investigators to study the biology of mechanisms of injury that can be generalized across species and are thus by inference referable to humans. Often unrealistic levels of exposure are required to produce a reasonably reproducible effect, and thus extrapolation to exposure levels found in humans is difficult. However, understanding the mechanisms of injury provides direction and

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guidance for the kinds of studies that might be carried out in humans.

Human controlled clinical exposure studies conducted at relatively low, and presumed safe, levels can provide insight into the exposure-response relationship between a particular agent and a measured physiologic response. Of necessity, the response must be short lived and, thus, can be interpreted only as being applicable to short-term effects. However, arguing by analogy with the health impact of long-term exposure to cigarette smoking, repeated short-term exposure might have a significant long-term effect. In patients with underlying significant respiratory disease, even short-term effects could influence morbidity from their underlying disease.

Long-term effects in humans can be studied only with the use of *population-based epidemiologic studies*. Both exposure-response relationships and the magnitude of the potential impact can be established from these studies. However, because these studies can never be defined as planned exposures, the findings must be interpreted as identifying associations that may be causal only if they are consistent, reproducible and follow a temporal pattern that makes biologic sense.

The results of the specialty conference suggest some sound basis for concern. These findings will be briefly summarized.

Animal Experimentation

Short-term exposure to ozone at levels only two times those commonly seen in the ambient environment lead to hyperplasia and hypertrophy of ciliated bronchiolar epithelium of nonhuman primates. This results in replacement of the ciliated cells with alveolar type II (Clara) cells, a recognized basic mechanism of response of the lung to relatively nonspecific injury. Exposures lasting up to 90 days at roughly five times the current 24-hour ambient standard result in evidence of chronic bronchiolitis. There is some adaption because the lesions do not appear to progress even if exposure is continued for as long as one year. These abnormalities, however, do appear to account for an increase in airways resistance that has been measured after one year of exposure.

In a wide variety of species (including humans exposed to toxic levels of NO_2 in the occurrence of silo-filler's disease), NO_2 at concentrations varying from 40 to 200 ppm can result in death. Vascular congestion, edema and bronchiolitis can be produced readily in all species from short-term exposure of 10 or more ppm. However, even at levels of exposure of only a few parts per million, transient changes in the ultrastructure of alveolar cells and basement membranes can be shown. Long-term exposure to five times the current ambient annual standard of NO_2 does not cause significant morphologic damage on its own; however, combined with only modest levels of NO_2, pathologically detectable emphysema has been found in beagle dogs three years after exposure was terminated. What is also clear is that in terms of direct and permanent lung cell injury, NO_2 is only a tenth to a twentieth as potent as ozone.

Another mechanism, which involves the alteration of the bactericidal capacity of alveolar macrophages, can be demonstrated following exposure of multiple species of rodents to ozone or NO_2. With increasing exposure, there is progressive impairment of ingestion and intercellular killing of ingested nonpathogenic microorganisms by the exposed alveolar macrophages. At concentrations of ozone or NO_2 that produce these results, there is no impairment of mucociliary clearance. Pathogenic microbes result in increased mortality from infection. Furthermore, long-term exposure to levels of ozone not much more than twice those occurring in the ambient environment can induce excess mortality in these rodents. Since the defense mechanism of the lung for the maintenance of sterility in lower airways is similar in rodents and humans, there is every reason to believe that a similar mechanism might be involved in humans at some levels of exposure.

Human Clinical Exposure Studies

As indicated, human clinical studies afford the opportunity to assess exposure-response relationships. For both ozone and NO_2, there are dose-response patterns. However, since the site of action is different for each pollutant and dose is so hard to measure, the shape of the exposure-response curve for either ozone or NO_2 has not been adequately evaluated. What is clear is that at some point along the exposure-response curve, clinical symptoms and physiologic changes can be readily noted, particularly for ozone.

Recent physiologic studies of exercising athletes have shown an exposure-response relationship to relatively low levels of ozone. The effect produced by ozone appears to be similar to that produced by equivalent ambient oxidant levels. Similar effects have not been shown with NO_2. Combined exposure to both ozone and NO_2 does not appear to potentiate the effects of only ozone.

Bronchial challenge studies using methacholine or carbachol with and without prior exposure to ozone or NO_2 confirm the difference in potency of these two agents. Nevertheless, the data suggest that at relatively high exposure levels NO_2 does induce increased bronchial reactivity. At more realistic levels of exposure, however, it is not clear that NO_2 increases morbidity among sensitive subjects.

Epidemiologic Data

In spite of reviewing more than 40 citations of epidemiologic papers, this part of the seminar contained the weakest argument for a significant health effect. Some of the studies cited had no adequate estimates of exposure. Epidemiologists have relied for too long on regional air-monitoring sampling schemes not specifically designed for health effects studies to estimate exposure. Often these exposure estimates are so crude as to provide misinformation rather than just misclassification and, in general, should be summarily rejected. In those studies in which exposure was monitored, the level of that exposure was often modest and present for only relatively brief periods of time. The few studies that have attempted to use rather unique exposure settings have also produced equivocal results. In part this equivocation is caused by issues of confounding and, in part, because the "signal-to-noise ratio" of the kinds of effects being sought is so small as to make it extremely difficult to identify an effect as significantly greater than the variability of the measurement. The sample sizes studied were inadequate to detect an effect of the magnitude that could be reasonably expected. Considerably larger population groups would be necessary, but it is in just such large population groups that it is difficult to make confident measures of exposure.

With these caveats and criticisms, one can consider those few studies that do provide insight into the possible magnitude

of the health impact of exposure to these agents. In this setting it is important to keep in mind what has been learned in animal experimental studies and in the controlled chamber studies because those results provide the plausible hypotheses that can be tested in free-living population groups.

Obviously, subjects with hyperreactive airways could be anticipated to be at increased risk from exposure to either ozone or NO_2. There is suggestive evidence that at least subgroups of asthmatic persons are at increased risk of attack from exposure to elevated ambient levels of oxidant pollutants. Furthermore, transient changes in pulmonary function (peak expiratory flow) have been shown in normal children exposed to transient changes in ozone levels.[2]

There are no longer substantial community-wide exposures to NO_2 because of the reduction of the munitions industry in this country. However, NO_2 is a significant indoor pollutant, generated for the most part by the domestic use of natural or liquid propane gas. Indoor exposure to gas cooking stoves has been identified as a source of exposure to NO_2 among a number of other pollutants. To date, the results of health effects studies, whether in the assessment of the potential for increase in infectious disease rates or of the effects on lung function, are equivocal but suggest an effect on young children. What is encouraging is that the potential for an effect of indoor exposure to NO_2 is under investigation by a number of approaches, and definitive results should be forthcoming shortly.[3]

What is one to conclude from review of the seminar data? As physicians and scientists, we are often asked both by patients and by policy makers to help make decisions that have significant impact on both our patients' and our communities' resources. Should a patient buy or replace an unvented gas stove? Given an option, should a patient move into or out of a given community exposed to a specific pollutant? How much should a community pay to clean up further an environmental source of pollution? None of the answers to these and other relevant questions are dealt with specifically in the seminar proceedings. What does come across is that nothing is for free and the willingness to pay requires the availability and dissemination of knowledge.

In regard to ozone and NO_2, the circumstantial evidence is considerable. The risk is not trivial, but also not overwhelming. Specific persons do need to be protected. The pathophysiologic mechanisms of injury are understood, and appropriate protective strategies could be undertaken.

Policy decisions that involve willingness to pay will require additional epidemiologic data. These data are not likely to come from the general kinds of epidemiologic studies done to date, but will require carefully designed multidisciplinary efforts that involve longitudinal data collection on relatively large and carefully selected population groups, along with quantitative monitoring of specific exposure. These kinds of studies are currently under way, and one can predict that another seminar conducted five years from now on this topic will provide specific risk estimates and risk assessment for defined population groups.

Meanwhile the evidence is consistent enough to advise specific patients on avoidance techniques. For ozone and NO_2, that avoidance comes in different forms. Ozone is an outdoor pollutant that is tracked by local health officials. Avoidance occurs by reducing exercise and staying indoors as much as possible when ozone or oxidant levels are high. For NO_2, besides proximity to automobile traffic, the major sources are indoors (unvented gas stoves, kerosene fires and space heaters). Particularly in houses with symptomatic children or adults with chronic obstructive pulmonary disease, exposure to these sources should be minimized.

Finally, and to date unproved, is the relation between exposure to relatively low levels of oxidant and NO_2 and the subsequent development of chronic obstructive pulmonary disease (COPD). Studies of the natural history of the development of COPD suggest that the disease does not develop in all subjects exposed to a putative agent. Varying susceptibility related to either genetic or early environmental impacts places people at different risk for disease from exposure to the more hazardous pollutant (cigarette smoke) in mid-adult life.[4] To implicate or exclude ozone or NO_2 in the development of increased risk to subsequent COPD will require considerably more data than are currently available.

At present the task for practicing physicians is clear. We must attempt to understand the nature and applicability of the data being collected. We must explain to our patients the implications of the studies that inevitably will be reviewed in the popular press and discuss with them the difficulty of extrapolating from animal studies and human controlled exposures to free-living human population groups. Whether ozone and NO_2 will affect the subsequent development of most cases of COPD becomes a moot point if we can prevent our patients from smoking cigarettes. We should, therefore, not be sidetracked from this important public health problem, and must use every opportunity available to refocus the problem where it belongs. Unless we are successful in dealing with personal pollution (cigarette smoking), the impact of dealing with environmental pollutants (such as ozone and NO_2) will not be detectable and may become a futile and expensive exercise.

Meanwhile, investigators working in the air pollution-health effects field have the responsibility to present in a clear and precise fashion both the encouraging and disappointing aspects of their data. Certainly, in 25 years a great deal has been learned. However, the precipitating problem of how we provide the necessary power to transport people over both short and long distances will not disappear. For the foreseeable future, the source of that power will be fossil fuels, and the consumption of fossil fuel will inevitably lead to by-products that are the pollutants of concern. Control technology is part of the answer, but an informed and knowledgeable public, who will have to make choices, is a necessary part of the decision-making process. Informed physicians will have a key role in the intelligent transfer and interpretation of that information.

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Epitomes

Important Advances in Clinical Medicine

Emergency Medicine

The Scientific Board of the California Medical Association presents the following inventory of items of progress in emergency medicine. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, research workers or scholars to stay abreast of these items of progress in emergency medicine that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Emergency Medicine of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to Division of Scientific and Educational Activities, California Medical Association, 44 Gough Street, San Francisco, CA 94103

Autotransfusion

AUTOTRANSFUSION was first used in 1818 by Blundell for postpartum hemorrhage. The Vietnam War showed the need for immediate availability of compatible blood in many cases of major trauma. Cardiopulmonary bypass procedures have provided necessary clinical experience and experimental data. Now cases of civilian trauma are benefiting from the use of autotransfusion.

In an emergency department, autotransfusion offers immediately available blood at room temperature for an exsanguinating patient. Blood supplied by autotransfusion is fresh and compatible. Procoagulation factors VIII and IX, absent in bank blood, are at nearly 100% of normal activity. Platelet levels are low but significantly higher than in bank blood. Hypofibrinogenemia is a consistent finding; however, there is no evidence of coagulopathy until half a patient's blood volume has been retransfused. In transfusions of less than 4,000 ml, the liver can replenish the circulation with fibrinogen. Studies of systemic effects showed no difference in prothrombin, partial prothrombin time, plasma hemoglobin concentration, plasma fibrinogen concentration and fibrinogen-fibrin degradation products in autotransfusion recipients versus recipients of bank blood.

Erythrocyte hemolysis may occur with vacuum collection pressures of greater than 60 mm of mercury. This appears to be well tolerated. No cases of renal failure have been reported.

Sepsis from contaminated blood has been a major concern in autotransfusion. There seems to be minimal risk from isolated hemothorax. Even blood with enteric, biliary or urinary contamination seems to be safe with the administration of broad-spectrum antibiotics. Most authorities consider autotransfusion with contaminated blood advisable only in the most dire circumstances.

Microemboli with pulmonary and renal complications have occurred. This problem is alleviated with micropore filtration. Air embolism has been extremely rare with gravity-assisted reinfusion techniques.

The most common device in emergency departments is the Sorenson autotransfuser. There are many modifications of this basic type of system. It is inexpensive, rapidly assembled and easy to use. Systems incorporating cell washers and pumps are more appropriate in an operating room where a technician is available.

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Ciguatera Toxin Poisoning

CIGUATERA (from *cigua,* the poisonous turban shell snails of the Spanish Antilles) toxin poisoning follows the ingestion of tropical and semitropical benthic marine fish. Most cases involve the barracuda (family Sphyraenidae), red snapper (genus *Lutjanus*), jack (family Carangidae), grouper (family Serranidae) and parrot fish (family Scaridae), which accumulate a series of at least five toxins that originate in the dinoflagellate *Gambierdiscus toxicus.* Larger animals in the food chain assume greater toxicity. The toxin is without taste and is impervious to gastric acid, freezing temperatures and extreme heat.

The toxin, which appears to be composed of lipid-soluble and water-soluble components, possesses cholinomimetic and anticholinesterase activity. Major toxic effects have been linked to sustained depolarization of nerve and muscle membranes, caused by a putative blockade of calcium sites that regulate the passive sodium pores.

Symptoms of ciguatera toxin poisoning are noted from 15 to 30 minutes after ingestion, with rare delay of as long as 24 hours. Gastroenteritis is followed by pruritus, paresthesias,

the pathognomonic reversal of hot and cold sensation, hypersalivation, odontalgia, dysphagia, malaise, myalgias, diffuse or focal weakness, muscle fasciculations, tremor, athetosis, meningismus, ataxia, blurred vision, seizures, bradycardia, hypotension, ascending paralysis, coma and respiratory failure. Fatalities are rare. Vomiting and diarrhea resolve in from 24 to 48 hours; dysesthesias and subtle neurologic abnormalities may persist for as long as two months.

Therapy is supportive. In managing a case of acute ingestion, the use of magnesium-based cathartics should be avoided, as they may augment a calcium channel blockade. Bradyarrhythmias are responsive to administration of atropine sulfate. An intravenous infusion of calcium gluconate for hypotension has been recommended, but this treatment is as yet empirical.

The lipid-soluble component can be extracted from fish flesh with serial solvent elutions. A radioimmunoassay can detect ciguatera toxin in fish flesh, but does not identify a human syndrome. Although counterimmunoelectrophoresis of toxic (human reaction or in vivo mouse bioassay) fish extracts and human serum confirms toxic fish specimens, specimens of both immune and nonimmune human serum show precipitin reactions with toxic extracts. Therefore, it is not yet possible to conclude that affected persons have ciguatera toxin-specific antibody. Until further tests are available, the diagnosis of ciguatera toxin poisoning must be made clinically.

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The Use of Hemoperfusion to Treat Poisoning and Drug Overdose

THE GOAL in treating a case of poisoning is to limit the effects of the poison and thus prevent death or serious complications. The simplest way to prevent toxic effects is to interrupt absorption from the gastrointestinal tract with gastric-emptying procedures and adsorption with activated charcoal. Once the toxin has been absorbed into the body, its toxicity may be countered by intensive supportive care including airway protection, assisted ventilation and fluid management. These widely used treatments have reduced the mortality of poisoned patients requiring hospital care to less than 1%. More invasive and complex methods such as hemoperfusion, which increases the elimination of poisons from the system after absorption, have been widely used but poorly studied.

Hemoperfusion is done by passing a victim's blood directly over an adsorbent material (charcoal or resin) and returning the filtered blood to the patient. Standard hemodialysis roller pumps and vascular catheters are used, and the patient must be receiving heparin. Flow rates of as high as 300 ml per minute can be achieved, and when there is good extraction by the adsorbent column, significant removal is possible for some toxins. However, for a drug or poison to be effectively eliminated from the body, it must be readily accessible for such blood "cleansing"—that is, it should not be highly tissue bound or otherwise sequestered outside of the bloodstream. Thus, drugs with very large volumes of distribution, such as digoxin, tricyclic antidepressants, phenothiazines and narcotics, are unlikely to be significantly removed, whereas those with small volumes of distribution, such as theophylline, phenobarbital, salicylate and acetaminophen, are readily available for elimination.

Before undertaking hemoperfusion, one must decide whether the benefits of accelerated toxin removal outweigh the risks of vascular access and anticoagulation. For most cases of intoxication, simple supportive measures are satisfactory. Situations that might prompt the use of hemoperfusion include clinical deterioration despite maximal supportive measures; the presence of a known lethal dose or blood concentration, or the loss of normal excretory mechanisms, such as with renal or hepatic failure.

Hemoperfusion may be undertaken for phenobarbital overdose when hypotension and metabolic acidosis persist despite warming, fluids and pressors. It is indicated for theophylline intoxication when there are intractable seizures or when blood concentrations are very high (above 100 mg per liter, or 60 mg per liter in patients with chronic, accidental overmedication). It is currently recommended for cases of paraquat poisoning—even though the elimination rate is low—because of the lethality of untreated intoxication. Although hemoperfusion has been used for cases of tricyclic-antidepressant overdose, it has not been shown to remove significant amounts of the drug or its metabolites.

Although hemoperfusion is a useful method of removing some toxins, it has limited indications. Complications include vascular trauma from catheter placement, local hematomas, air embolism, intracranial bleeding and thrombocytopenia. Repeated-dose oral activated charcoal may eventually prove to be a preferable method of accelerated elimination in some patients, especially those with less severe poisoning or with contraindications to heparinization.

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The Computer as Physician? Automatic External Defibrillation

RECENT EVIDENCE has suggested rather convincingly that early external defibrillation is the single most important factor in successfully reversing out-of-hospital cardiac arrest. However, many communities have neither the patient volume nor the financial resources to initiate and maintain full advanced life-support skills in their emergency medical services personnel. Basic emergency medical technicians can be trained to recognize and treat cases of ventricular fibrillation, and clinical studies have shown improvement in hospital discharge rates of around 15% for cardiac arrest victims so treated. Unfortunately, such training is not inexpensive and requires frequent refresher courses. A computerized,

self-contained device (Heart Aid, Cardiac Resuscitator Corporation, Wilsonville, Oregon) that automatically identifies ventricular fibrillation and applies countershocks is now commercially available. This automatic defibrillator requires very little training to use and costs about as much as a standard monitor-defibrillator. Electrodes are applied to the tongue and epigastrium, the machine is activated and cardiopulmonary resuscitation interrupted for a maximum of 15 seconds. The device then analyzes the electrocardiographic findings and checks for spontaneous respirations (via a breath sensor in the mouth). Countershocks are delivered when appropriate and results analyzed. Prerecorded voice messages prompt emergency medical services personnel to assist respirations, check for pulses, continue cardiopulmonary resuscitation and so forth. Rozkovec and co-workers showed the safety and efficacy of the tongue-epigastric route for cardioversion, delivering charges of up to 320 J. Jaggarao and colleagues treated 11 consecutive patients in cardiac arrest with the automatic defibrillator: six were successfully defibrillated and resuscitated and five were discharged alive from hospital. The device also has an automatic external pacing function that has not been as extensively studied. Clinical trials are ongoing in many states, and results continue to support the addition of the automatic external defibrillator as a valuable tool for emergency medical services personnel.

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Aeromedical Emergency Care

ROTORCRAFT AEROMEDICAL emergency care was born during the closing days of World War II when the early Sikorsky helicopters were used to evacuate casualties in the European theater. The extensive use of rotorcraft for this purpose did not take place until the Korean conflict, during which time both the Army and Air Force used Bell 47s to evacuate casualties to Mobile Army Surgical Hospital (MASH) units. This expertise was extended to the civilian sector following the close of the Korean conflict in the form of dual-purpose public safety services in which rotorcraft was used for both public safety missions, such as law enforcement and fire suppression, and emergency medical service missions. Due to the dual service nature, the medical expertise of the flight crews was very limited. In the early 1970s, rotorcraft began to be based at hospitals and fully committed to emergency medical service missions. Because a rotorcraft was stationed at a hospital, the medical flight crews could be selected from the more experienced medical personnel within the institution. Flight nurses became the mainstay of these services and brought a level of medical expertise to the field heretofore unseen. At that time, paramedics could place peripheral intravenous lines, administer a limited number of drugs and use the defibrillator/cardioverter. Flight nurses, on the other hand, were trained to place endotracheal tubes, thoracostomy tubes, central intravenous lines, administer a wide spectrum of drugs and do all those procedures paramedics could do. In 1976 physicians were placed on hospital-based rotorcraft emergency care services and the potential for bringing even a higher level of expertise to the field became limited only by the training of a physician. The capability to do cricothyroidotomy, pericardiocentesis, place cranial trephines and even perform open thoracotomies in the field became a reality.

Recently, the impact of these services on mortality from blunt trauma has been investigated in two studies. In the first, the mortality of 150 consecutive trauma patients treated at the site of injury and transported to a trauma center by standard land prehospital care services was compared with that of 150 consecutive trauma patients treated at the site of injury and transported to the same trauma center by a rotorcraft aeromedical service staffed by a physician and nurse. A statistical analysis designed to predict mortality based on injury severity showed that the mortality of the land group was statistically no different from that of a large index trauma patient population treated at a major trauma center. There was a 52% reduction in predicted mortality of the aeromedical group, which was statistically significant ($P < .001$).

In the second study the same methodology was used; the mortality of 1,273 patients treated and transported by seven different hospital-based rotorcraft aeromedical services was compared with that of more than 3,000 patients treated by land emergency medical services and transported to 45 trauma centers across the United States. This study showed a 21% reduction in the predicted mortality, which was also statistically significant ($P < .001$).

In both studies the patients treated by the aeromedical services were more seriously injured than those treated by the control services. In addition, of those patients who died, death was caused by more severe injuries in the aeromedical group; of those patients who survived, survival was despite more serious injuries in the aeromedical group. The major reduction in predicted mortality was in those aeromedical patients who had suffered more severe injuries, representing less than 20% of all trauma patients treated by these services.

In conclusion, it appears that hospital-based aeromedical emergency care services may reduce mortality of at least blunt trauma patients, and that the most seriously injured patients seem to receive the greatest benefit from these services.

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Calcium Channel Blockers in Emergency Medicine

OVER THE PAST few years a new class of drugs, the calcium channel blockers, has been introduced. As a group, these drugs inhibit the intracellular movement of extracellular calcium through voltage-dependent membrane channels. Because cardiac and vascular smooth muscle is particularly

dependent on calcium for its function, it is not surprising that calcium channel blockers have specific value in the treatment of cardiovascular disease. The calcium channel blockers most recently released in the United States for commercial use are nifedipine and diltiazem hydrochloride.

At the recommended dosage, nifedipine, unlike verapamil hydrochloride, has no effect on the sinoatrial or atrioventricular node. In addition, it does not significantly depress myocardial contractility. It can, therefore, be used safely in patients with conduction abnormalities and congestive heart failure. Its major target tissue is vascular smooth muscle. Of the calcium channel blockers currently available, nifedipine is the most potent vasodilator. Its use in the emergency room is dependent on this effect. Nifedipine produces coronary artery dilation, rendering it very effective for treating vasospastic (Prinzmetal's) angina. Given sublingually, it is simple to administer and acts rapidly. Nifedipine also induces systemic vasodilation and is emerging as an effective drug for control of cases of hypertension in the emergency room. Unlike other calcium channel blockers, tachyphylaxis to its antihypertensive action has not been reported. For patients with diastolic pressures lower than 110 mm of mercury, 10 mg given sublingually or orally usually achieves good control. For diastolic pressures greater than 110 mm of mercury, 20 mg is given. An additional 10-mg tablet can be given after one hour if necessary. A mild increase in heart rate of approximately ten beats per minute may result.

Long-term use of nifedipine does not produce sodium retention, plasma volume expansion or renin release. Combining it with propranolol hydrochloride provides additional antihypertensive control, blocks the reflex increase in heart rate and permits twice-a-day dosage of nifedipine. Methyldopa can also be used but the nifedipine must be given every six hours. Mild pedal edema can be managed with the use of diuretics. Because vasodilation with subsequent afterload reduction decreases myocardial oxygen consumption, nifedipine is also effective in treating classical angina; it is infrequently used in emergency departments for this indication, however, because of the efficacy of nitroglycerin.

Diltiazem is the latest calcium channel blocker to be released. Its actions are intermediate to those of verapamil and nifedipine. Diltiazem is equivalent to verapamil in depressing atrioventricular node conduction, but produces less refractory period prolongation. Therefore, it is effective in treating paroxysmal supraventricular tachycardia and atrial fibrillation or flutter, but may be safer than verapamil in patients receiving digoxin or those with atrioventricular nodal disease. However, diltiazem has a greater inhibitory effect on the sinoatrial node and is more dangerous in patients who have sick sinus syndrome. Diltiazem is indicated for the treatment of cases of both types of angina, producing more vasodilation than verapamil but less than nifedipine. In addition, diltiazem has less negative inotropic activity than verapamil. Although possessing some theoretic advantages, diltiazem has not proved clinically superior to the other calcium channel blockers in the emergency setting. Therefore, it has no specific indication in emergency medicine at the present time. Except for its use in treating congestive heart failure, it has the same contraindications as verapamil.

None of the calcium channel blockers currently available are effective in cerebral salvage after cardiac arrest. However, newer calcium channel blockers, such as lidoflazine and flunarizine hydrochloride, have prevented neurologic deterioration after brief periods of global ischemia in laboratory animals. Studies are currently in progress evaluating their effects in humans.

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New Diagnostic Tests of Blunt Cardiac Trauma

MYOCARDIAL CONTUSION is an elusive clinical disorder. The absence of both a simple, accurate screening test and a diagnostic gold standard causes confusion. Moreover, no good clinical studies accurately define short- and long-term morbidity and mortality.

The workup of patients in an emergency department who have possible cardiac contusion includes a history, a physical examination and electrocardiography. The reported sensitivity and specificity for electrocardiographic prediction of cardiac contusion are variable and depend on the diagnostic criteria used. If the mechanism of injury is of high risk for cardiac contusion, the patient is admitted and CPK-MB isoenzyme studies are done. The presence of CPK-MB isoenzyme was initially thought to represent the gold standard for diagnosing cardiac contusion; recent reports, however, have shown a lack of specificity in patients with multiple trauma, even when CPK-MB ratios are used. Nevertheless, it does appear to be the most sensitive of currently used screening tests, and a clinical suggestion of cardiac contusion warrants that both an electrocardiogram (ECG) and CPK-MB values be obtained.

Radionuclide scans with technetium Tc 99m pyrophosphate have a low sensitivity for cardiac contusion and should no longer be used.

Recently, two relatively new diagnostic methods have shown promise: multiple-gated acquisition (MUGA) radionuclide scans and two-dimensional echocardiography. The MUGA scan is useful in determining whether continuing hemodynamic instability may be due to cardiac contusion.

Most patients suspected of having a cardiac contusion are young and otherwise healthy. Consequently, segmental wall dysfunction on MUGA scan is felt to be specific for cardiac contusion in young, previously healthy trauma victims.

Advantages of the multiple-gated acquisition scan include

- Cardiac dysfunction caused by cardiac contusion can be documented and a patient appropriately managed;
- Serial MUGA scans document the course of hemodynamic compromise. In one large series 27 of 32 patients with abnormalities on a MUGA scan subsequently had improvement or resolution of their wall motion defect on follow-up scans, indicating recovery of the contused myocardium;
- The test is relatively noninvasive and can be done with a portable γ-camera in an intensive care unit.

Disadvantages of the MUGA scan include the following:

- Lack of 24-hour availability in most hospitals;
- Hypovolemia may cause the scan to be falsely positive due to decreased cardiac filling;
- Older patients with preexisting cardiac disease may have positive findings from nontraumatic causes;
- The predictive relationship between the scan's findings and morbidity and mortality has not been clearly established.

Two-dimensional echocardiography may prove to be of use in the future; a recent report indicates that two-dimensional echocardiography can detect complications of cardiac contusions.

Emergency physicians must continue to rely on "clinical suspicion" and ECG findings in screening patients with possible cardiac contusion. Identifying CPK-MB isoenzymes is best used to screen trauma patients requiring hospital admission. For hemodynamically unstable patients, portable MUGA scans can be done in an intensive care unit. With hemodynamic monitoring, MUGA scans provide the best current method for determining the presence of hemodynamic instability due to cardiac contusion.

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Conjunctival Oximetry

MAINTAINING ADEQUATE tissue oxygenation to prevent anaerobic cellular metabolism is a major function of the cardiorespiratory system. Clinical assessment of this important physiologic variable was not possible before the development of miniaturized polarographic oxygen electrodes that could be placed directly on peripheral tissue sites. Initially, transcutaneous oxygen sensors were used; these sensors required heating to liquefy the stratum corneum so that oxygen could diffuse from the subcutaneous capillary bed to the oxygen electrode. Transcutaneous sensors introduced artifacts in the measurement of tissue oxygenation because the heated electrode produced increased tissue metabolism, reactive hyperemia and a rightward shift of the oxyhemoglobin disassociation curve in the area beneath it. In addition, the prolonged stabilization period (longer than ten minutes) and the relatively slow reaction time to clinical events prevented widespread use of the transcutaneous oxygen sensor in emergency medicine.

The recent development of a conjunctival oxygen sensor has permitted direct measurement of tissue oxygenation ($Pcjo_2$) without heating artifacts. The miniaturized oxygen electrode is mounted on a polymethyl-methacrylate ocular conformer, so that on insertion the electrode lies against the lateral, superior palpebral conjunctiva. Because no stratum corneum is present on the conjunctiva, an unheated oxygen electrode is used. The capillary bed is located about 30 microns from the conjunctival oxygen electrode and $Pcjo_2$ values have been calculated to be from 5 to 10 torr less than capillary oxygen tension. The conjunctival sensor can be rapidly inserted without patient discomfort, and can be left in place for up to 24 hours. Stabilization of the conjunctival sensor is almost immediate, so that meaningful values of conjunctival oxygen tension are available within 60 seconds of insertion. The response time of the conjunctival sensor to physiologic state changes is rapid, usually from 30 to 60 seconds.

In normovolemic patients with a normal cardiac output, $Pcjo_2$ is about 70% of partial pressure of arterial oxygen (Pao_2), and these two variables track each other closely. In this setting, $Pcjo_2$ can be used as a continuous, noninvasive monitor of Pao_2 and respiratory state.

Because the conjunctival sensor measures tissue oxygenation at a peripheral site where perfusion is affected at an early stage of physiologic instability, measuring the $Pcjo_2$ can identify important alterations in clinical state before other noninvasively measured variables, such as blood pressure, respond to the changing situation. Decreases in peripheral tissue oxygen delivery and perfusion due to factors such as hypovolemia or poor cardiac function will result in disassociation of $Pcjo_2$ and Pao_2.

In a series of normotensive trauma patients with no history of cardiac disease, a $Pcjo_2/Pao_2$ ratio of less than 0.5 predicted an intravascular volume deficit of 15% or greater. Normalization of the $Pcjo_2/Pao_2$ ratio—that is, to values greater than 0.5—occurred with volume resuscitation. Deterioration of previously stable $Pcjo_2$ values, presumably reflecting decreasing cardiac output, preceded cardiac arrest by three to four minutes in critically ill patients; return of a viable cardiac rhythm was accompanied by a rise in $Pcjo_2$ from the values present during cardiopulmonary resuscitation.

The $Pcjo_2$ provides a unique measure of physiologic state, capable of detecting alterations in a patient's clinical condition before traditionally measured indicators show changes. Conjunctival oxygen measurement represents a major advance in noninvasive monitoring.

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Viral Hepatitis Type B Vaccine

VIRAL HEPATITIS type B attacks an estimated 200,000 people a year in the United States. Although most patients recover completely, in 1% to 2% of those admitted to hospital, fulminant hepatitis develops and 6% to 10% become chronic carriers of the disease.

The eight-year-old viral hepatitis type B (HBV) vaccine consists of a non-disease-producing hepatitis B surface antigen (HBsAg) protein extracted from the plasma of asymptomatic carriers. Multiple purification processes effectively inactivate all other known infectious agents. The vaccine inhibits the occurrence of disease or modifies its manifestations if given before or during the incubation period.

The HBV vaccine is recommended as routine immuniza-

tion for people at high risk for infection. These include health care workers in regular contact with blood or body fluids, especially surgeons, pathologists, oral surgeons, dentists and hygienists; operating room, intensive care unit, hemodialysis unit and emergency room staff, and hematology and blood bank technicians and phlebotomists. Other high-risk groups include sexually promiscuous populations (especially homosexual men), intravenous drug users, hemodialysis patients, residents and staff of mental institutions, prisoners and residents of viral hepatitis type B endemic regions. It is recommended that the HBV vaccine be given to household and intimate contacts of acutely infected persons. Recommended postexposure prophylaxis for known exposure to viral hepatitis type B has recently been modified such that the vaccine should be given along with an initial dose of hepatitis B immune globulin (HBIG) (at a separate site) to patients at risk; subsequent doses of the vaccine are given at one and six months, while the usual second dose of HBIG is no longer required. A booster of vaccine is recommended after five years. The vaccine can also be given to neonates whose mothers are HBsAg-positive; the risk to the fetus should be negligible. Pregnancy should not be considered a contraindication for vaccination for women at risk.

No serious side effects related to the vaccine have appeared in more than 200,000 recipients since testing began. Pain at the injection site and low-grade fever have been the only side effects noted in controlled trials of HBV vaccine. No cases of hepatitis B or non-A, non-B hepatitis have developed from vaccination. Similarly, there is no evidence that *any* cases of acquired immunodeficiency syndrome (AIDS) have been caused by vaccine administration, and, indeed, the incidence of AIDS is less in vaccine trial recipients (composed of patients at high risk for AIDS) than in matched controls who received placebo.

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Nonoperative Management of Fingertip Amputations

NONOPERATIVE MANAGEMENT of fingertip amputations has been described in the literature for more than ten years and has now become a generally accepted alternative to surgical repair. Nonoperative treatment—allowing a fingertip to heal by secondary intention—has achieved cosmetic and functional results that are consistently superior to split-thickness grafting techniques. Local flaps such as the Kutler V-Y flap, crossed-finger flaps and volar-advancement flaps offer early coverage of a finger, but the complication rate and long-term results are poorer than with nonoperative management. Superior results have occurred in prospective trials in which the wound was allowed to heal secondarily.

Nonoperative management provides the further advantage of preserving maximum finger length by removing the necessity in most cases of rongeuring back the exposed bone to provide skin coverage surgically. Nevertheless, some patients who need skin coverage to return to work may elect a surgical procedure, even if some further shortening of the finger is required.

The technique of nonoperative treatment involves debridement of nonvital soft tissue only, followed by an occlusive dressing (antibiotic, petrolatum gauze, gauze bandage) for 48 hours. Warm-tap-water soaking four times a day for 10 to 15 minutes is then instituted. The wound may be covered with two plastic bandages between soakings (one over the end of the finger, and the other around the first to keep it in place). The wound heals in two to three weeks in cases of pulp amputation and four to eight weeks in cases of more extensive injury involving exposed or protruding bone. In many cases, the patient can return to work in two to three days with a protective splint, if needed. Frequent bandage changes and soaking serve to remove any exudate and debris. The prophylactic use of antibiotics is generally not necessary except in grossly contaminated wounds. Joint stiffness can be prevented by active range of motion of all finger joints during soaking.

Healing occurs as soft tissue migrates over any exposed bone and is covered by the advancing epithelial margin. The result is a fingertip with normal epithelium except for a small linear scar. Amputation neuromas rarely, if ever, occur. Sensation is generally excellent, as is cosmetic appearance. Most complications are related to nail deformity, which most often occurs when a significant portion of the bone under the nail bed has been lost. Such deformities may be eliminated by removing the nail matrix entirely (either at the time of injury or at a later date) if a patient so desires.

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The Use of Activated Charcoal in Cases of Poisoning and Drug Overdose

ACTIVATED CHARCOAL is widely used in treating cases of poisoning and drug overdose. A finely powdered product of the pyrolysis of wood pulp, the charcoal is "activated" by exposure to oxidizing gas at high temperatures to make a network of tiny pores. The total surface area of these pores is about 1,000 m^2 per gram of charcoal. Activated charcoal binds a variety of drugs and chemicals and thus may prevent their absorption from the gastrointestinal tract. The effectiveness of charcoal in preventing poisoning was shown by a French pharmacist in 1831 when he swallowed a lethal dose of strychnine along with 15 grams of charcoal without ill effect.

Charcoal (50 to 100 grams) is routinely given to poisoning victims after emptying the stomach with ipecac-induced emesis or gastric lavage. Unfortunately, persistent emesis after ipecac is given often delays the administration of charcoal for as long as two to three hours. Because charcoal

effectively binds many toxins, it has been suggested that simple administration of charcoal may eventually supplant ipecac-induced emesis in most poisoning victims. In fact, a recent study showed that the use of oral charcoal alone was superior to ipecac-induced emesis. Volunteers who ingested 2 grams of aspirin absorbed significantly less salicylate when treated only with activated charcoal compared with those who were given only ipecac. A third group treated with ipecac then charcoal showed aspirin absorption similar to the ipecac-only group. This was apparently because only two of ten receiving ipecac then charcoal were able to retain the charcoal due to persistent vomiting. Further studies will be needed before charcoal replaces emesis in routine poisoning management. Charcoal does not effectively bind some toxins, such as iron and probably alcohols. Also, the use of charcoal remains controversial in a case of acetaminophen ingestion when oral administration of the antidote, *N*-acetylcysteine, is contemplated.

Recently, interest has focused on the use of repeated doses of charcoal (15 to 20 grams every three to four hours) to enhance the elimination of some drugs and poisons. This may occur by interrupting enterohepatic or enteroenteric recirculation. A 50% reduction of the serum half-life of theophylline and phenobarbital has been recently found in volunteers given repeat-dose charcoal. To prove that orally administered repeat-dose charcoal does not simply bind unabsorbed ingested drug, Berg and co-workers gave volunteers phenobarbital intravenously and found the same reduction in serum half-life. This increased nonrenal elimination is thought to be due to a "back-diffusion" of drug across the intestinal villi to the intraluminal charcoal, resulting in what has been described as "gastrointestinal dialysis." A similar reduction in serum half-life with repeated-dose charcoal has been shown in patients overdosed on theophylline and phenobarbital. However, whether this has practical clinical benefit remains unknown. In a randomized study of phenobarbital overdose, for example, patients receiving repeated-dose charcoal awoke and were extubated no sooner than those getting a single dose of charcoal, even though the drug's elimination half-life was much shorter.

These findings are applicable to the management of poisoned patients. Orally administered activated charcoal remains a fundamental adjunctive therapy for gastrointestinal decontamination. It may eventually replace the use of ipecac as the best single treatment for a variety of ingestions. The contribution of the use of cathartics, emesis or lavage to gut decontamination remains unclear but each continues to be widely used. Repeated-dose charcoal enhances the elimination of several drugs and is currently recommended for overdoses of digitoxin, phenobarbital or theophylline.

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Large-Volume Fluid Resuscitation

THE TRADITIONAL APPROACH to resuscitating exsanguinating patients has called for multiple large-bore intravenous catheters. In the past five years the means to achieve higher flow rates and fewer intravenous (IV) sites have been reexamined.

Flow rates are linearly and inversely proportional to tube length, linearly proportional to pressure and logarithmically (to the fourth power!) proportional to the radius of the tube's lumen. These considerations have led to new intravenous strategies described herein.

The Seldinger (wire-guided) catheter, used in intensive care units, probably represents the single greatest advance. Using an 18-gauge needle, an obturator allows, with technical ease, step-up to an 8.5 French sheath. This sheath can be inserted into virtually any deep or superficial vein as long as it is not subject to bending (kinking or venous perforation may then occur). An experimental 14 French sheath with an internal diameter (ID) of 4.5 mm (French number divided by 3 equals the millimeter) has been used without adverse effect in the veins of dogs. Y sidearms are often a part of catheter sheaths. Though originally small bore, many are now manufactured with internal diameters to match the catheter sheath. This allows their successful use in volume resuscitation.

Because standard IV tubing for administering blood has an internal diameter of 3.2 mm, the tubing becomes a limiting factor when catheter sheaths much exceed 8.5 French (2.7 mm ID). Thus another strategy has been to increase tubing size. Though not yet commercially available, tubing of 6.4 mm ID has been tested in concert with an 8.5 French catheter sheath. Even though the internal diameter of this sheath (2.7 mm) is less than that of standard IV tubing (3.2 mm), flow was considerably enhanced by this system.

Another major advance has been the routine use of pressure infusion bags placed about the plastic IV bags. These simple, inexpensive and trouble-free devices safely increase infusion pressures to 300 mm of mercury. Their use increases flow rates two to three times over simple gravity flow. Experimentally, infusion pressures of 600 mm of mercury have been used in vitro. Current pressure infusion bags "red line" at 300 mm of mercury, though this cutoff point appears arbitrary.

Other innovations have been described. To accommodate the large flow through a 14 French catheter, a manifold fed by five IV systems has been described and operated successfully in dogs. The Bentley autotransfusion system has been used in concert with the 8F catheter sheath to produce flows two to four times those achievable by gravity alone.

The size of the vein cannulated is probably only rarely the limiting factor in flow rates, due to the considerable ability of veins to dilate. However, in an exsanguinated patient, the larger vein is clearly easier to cannulate. Thus use of the femoral vein has been described more often recently, with initially encouraging results. Removing vein size from consideration, a recent communication describes successful placement of the IV tubing directly into the right atrial appendage at open thoracotomy.

The current optimal results with these developments are as follows: Using a pressure infusion bag at 300 mm of mercury, standard IV tubing and an 8.5 French catheter, in vivo flow rates of 500 ml per minute are achieved. Experimentally, using the same catheter with 6.4 mm tubing under 600 mm of mercury pressure, flow rates in vitro of crystalloid exceeded 3,000 ml per minute!

A word of warning: In the confusion surrounding the resuscitation of an exsanguinating patient, massive volume overload becomes a real danger. Therefore, careful ongoing evaluation and monitoring of intravascular volume are mandatory.

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Diagnosing Cases of Ectopic Pregnancy

ECTOPIC PREGNANCY is the leading cause of maternal death in the first trimester of pregnancy. The total number of cases of ectopic pregnancy reported in the United States rose from less than 18,000 in 1970 to greater than 52,000 in 1980. Ectopic pregnancy is extremely difficult to diagnose clinically. More than half of all cases of ectopic pregnancy are missed at first presentation, more than two thirds of ectopic pregnancies are ruptured at the time of diagnosis and 10% to 20% of patients suffer hypovolemic shock before definitive treatment is obtained.

Ectopic pregnancy must be suspected in all women of childbearing age presenting with either abdominal pain, irregular vaginal bleeding or both. While physical examination alone is unreliable in diagnosing ectopic pregnancy, culdocentesis has been found to be positive in from 75% to 94% of cases.

The two-minute agglutination-inhibition slide test for human chorionic gonadotropin (HCG) in urine remains negative until more than 1,500 mIU of HCG per ml is present, and from 30% to 50% of cases of ectopic pregnancy will be missed. The two-hour urine slide test is more sensitive (positive at greater than 250 mIU HCG per ml) but as much as 10% to 20% of cases of ectopic pregnancy may still be missed. Qualitative serum β-HCG assays are currently available, inexpensive, require only 30 minutes to do and give a positive report at a serum level of greater than 35 mIU HCG per ml. In a recent review of the literature, this test was positive in 439 of 445 (98.7%) cases of ectopic pregnancy. Quantitative serum β-HCG assays measuring levels less than 25 mIU per ml exist but are not widely available and require much longer to do.

Real-time ultrasonography is of great help in establishing the diagnosis of unruptured ectopic pregnancy. Its primary role lies in documenting a normal intrauterine pregnancy at about five to six weeks of gestation. Such a finding essentially excludes the possibility of ectopic pregnancy because the incidence of coexisting ectopic pregnancy and intrauterine pregnancy is about 1 in 30,000 pregnancies. Ultrasound examination may be of secondary importance in supporting a diagnosis of possible ectopic pregnancy by showing an adnexal mass or fluid within the cul-de-sac, or both. The ability to identify an adnexal mass as an ectopic pregnancy rather than a large ovarian cyst, hydrosalpinx, tubo-ovarian abscess or other cause of adnexal enlargement varies from center to center.

When a case of ectopic pregnancy is suspected, culdocentesis should be done. Positive findings on culdocentesis warrant a gynecologic consultation. A negative or nondiagnostic culdocentesis should be followed by pregnancy testing. A rapid two-minute urine pregnancy test that is positive should be followed by pelvic ultrasound examination. An ultrasound examination that does not show a normal intrauterine gestational sac should be followed by laparoscopy. If the two-minute urine pregnancy test is negative, it should be followed by a serum β-HCG test. A negative β-HCG test rules out an ectopic pregnancy in all but about 1% of cases. A positive β-HCG test should be followed by pelvic ultrasound study or laparoscopy. In one recently published study in which such an approach was used, all 16 patients with ectopic pregnancy from a study group of 81 patients suspected of having the disease were successfully identified.

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Editorials

Concerning Physicians' Responsibilities to Patients and to Society

A PHYSICIAN's first responsibility is to his or her patient. This has always been true and it still is true. But it is also true that in recent years society, in the form of third parties and some administrators of health care, has begun to exert pressures on physicians to consider the broader interests of society in their management of patient care. These pressures seem to derive largely from the desire and need of the payors and administrators to control or reduce the costs of care. In some situations, as when a physician is employed by a hospital or a health maintenance organization (HMO) for example, this can sometimes put a physician between a rock and a hard place—that is, caught between what may be in the best interest of a patient and what may be his or her own interest or that of an employer. This kind of situation raises the question, what are a physician's and the medical profession's responsibilities to society and how can the responsibilities to a patient be integrated with responsibilities to society?

The key to the answer to the above question would seem to lie in the special training of physicians and the special expertise of the medical profession. Society underwrites most of the cost of the training a physician receives, and society also licenses a physician to practice. In return physicians and the medical profession have a responsibility to use this training and expertise to fulfill a personal and professional obligation to society. At this moment in time there appear to be a number of ways this is or can be done:

(1) There is no doubt that physicians are licensed to practice by society with the expectation that they will use their training and expertise to care for those citizens who are sick or ill and need their care. And there is no doubt that society expects a physician to do what is right for a patient—that is, what he or she believes is best for the patient based on this training and expertise. In this sense, care of patients is actually a practicing physician's primary responsibility to society.

(2) It is reasonable to expect physicians and the profession as a group to be concerned with the costs of care, and indeed they are. But it is not reasonable to expect them to be other than advocates of the best interests of the persons under their care. Rather than respond to pressures to withhold or modify care they believe is needed or appropriate, it would seem that they could better apply their special training and expertise to evaluating the effectiveness of care, and eliminating those services or procedures that do more harm than good, have proved to be ineffective or to cost more than they are worth. A good housecleaning could reduce costs and even improve quality in patient care, and only physicians and the medical profession have the training and expertise to do this.

(3) Physicians and the medical profession should be willing and even expected to bring their special training and expertise to the decision-making process at every level of health care. This is not yet accepted as "de rigueur" by society, but experience suggests that when this does not occur mistakes are often made which might well have been avoided. This role for physicians and the medical profession could be more aggressively pursued by both the profession and by society.

(4) And finally as citizens, physicians can and should use their training and expertise to assist society in grappling with the social, economic and political problems that are the result of scientific and technologic progress in medicine as well as in other fields of endeavor that affect the health and well-being of people. Physicians, with their often intimate knowledge of human nature and human behavior, can many times contribute useful insights to a community or public dialogue concerning many of today's social, economic and political problems.

In summary it would seem that physicians' responsibilities to patients and to society are basically responsibilities to bring their special training and expertise to bear in behalf of patients, to improve health care and reduce its costs where this does not interfere with good patient care and where possible to help constructively with the social, economic and political problems that beset us all.

MSMW

Intracavitary Chemotherapy in Ovarian Cancer—An Investigational Procedure

THE DIRECT INSTILLATION of chemotherapeutic agents into malignant effusions is frequently successful in controlling the symptomatic reaccumulation of fluid. However, intracavitary chemotherapy is potentially more than a palliative treatment. In cases of malignant disease where the tumor is confined to a body cavity (primarily the pleural or peritoneal space), intracavitary chemotherapy may be capable of producing both complete and partial remissions even in patients whose condition has proved refractory to systemic (oral or intravenous) administration of antineoplastic drugs. The pharmacologic rationale, the technical considerations and the results of preliminary phase I trials of intracavitary chemotherapy have been reviewed by Markman in this issue of the journal. While the preliminary results of the clinical trials of intracavitary chemotherapy have been encouraging, particularly in establishing that the direct instillation of drugs into body cavities produces a pronounced pharmacologic advantage compared with the standard routes of drug delivery, intracavitary chemotherapy remains an investigational procedure whose efficacy needs to be established in carefully designed clinical trials.

In contrast to early trials of intracavitary treatment aimed at palliation of cases of malignant effusion wherein a drug was usually administered in a small volume, in recent clinical trials of intracavitary therapy a large volume (two liters) of drug has been used, which is administered through a semipermanent Tenckhoff catheter to allow for uniform drug distribu-

tion and to facilitate repetitive treatments. This new approach is based on pharmacologic modeling studies of the factors controlling the rate of movement of drugs across physiologic membranes,[1] which predicted that a pharmacologic advantage (a high drug concentration in the body cavity compared with those in the systemic circulation) would result from anticancer drugs with low lipid solubility and high molecular weight when they were directly administered into the peritoneal or pleural space.

Ovarian cancer is the malignant disease wherein intracavitary chemotherapy likely has its greatest potential therapeutic value. The majority of patients at the time of diagnosis have disease that has already spread outside the pelvis to involve distant peritoneal sites. Combination chemotherapy regimens produce responses in 60% to 80% of patients with advanced ovarian cancer; however, only 10% to 15% of patients who present with bulky disease will have a surgically documented complete remission (no residual cancer at a "second-look" laparotomy).[2] If intraperitoneal chemotherapy is capable of producing complete remissions in this patient population, it will represent an important therapeutic advance because patients with residual disease following a second-look laparotomy have not been successfully treated by other therapeutic modalities, including radiation therapy and second-line chemotherapy regimens.

Markman reviews a series of intraperitoneal drugs that have been evaluated in phase I trials in ovarian cancer patients, including methotrexate, 5-fluorouracil, mitomycin, doxorubicin hydrochloride, cisplatin, melphalan and cytarabine. In addition, the intraperitoneal administration of drug combinations has recently been reported.[3] The drugs have been administered via a semipermanent Tenckhoff dialysis catheter. While advances in the technology of intraperitoneal therapy and increased experience with these catheters have resulted in prolonged catheter maintenance in most patients, the catheters still are prone to the frequent development of obstruction to flow.[4] Depending on the drug, the dose-limiting toxicities in the phase I trials have been local (peritoneal irritation) or systemic (myelosuppression, mucositis). According to Markman, the pharmacokinetic studies have all shown a pharmacologic advantage for the intraperitoneal route of administration with concentration ratios of peak peritoneal to peak plasma levels ranging from 20 to 664. For the pharmacologic advantage to result in an increased therapeutic benefit, the drugs must penetrate into the tumor masses and result in increased cytotoxicity. However, the nature of the dose-response relationship for most of the drugs used in these phase I trials has not been clinically established. In addition, experimental evidence of drug penetration into tumors has been difficult to obtain and it appears that intraperitoneally administered drugs may be able to penetrate only into the outermost four to six cell layers of intraperitoneal tumors,[5] indicating that such therapy is likely to be most efficacious in patients with small volume disease.

While the optimal intraperitoneal drug, or drugs, remains to be established in ovarian cancer patients, the results of initial clinical trials suggest that cisplatin has the greatest potential therapeutic value of the drugs currently tested. Cisplatin has an important dose-response relationship both clinically and in experimental systems of ovarian cancer,[6] which suggests that the higher local drug levels achieved by the intraperitoneal route may produce an increase in cytotoxicity. In addition, the increased doses of cisplatin given intraperitoneally have resulted in blood levels comparable with those achieved by standard-dose cisplatin given intravenously.[7] Cisplatin also has not produced the local toxic effects associated with intraperitoneal administration of methotrexate,[8] 5-fluorouracil[9] and doxorubicin.[10] Cisplatin given intraperitoneally has also been biologically active in ovarian cancer patients who were refractory to standard therapy.[4] While administering doxorubicin and 5-fluorouracil intraperitoneally has also produced clinical responses in some patients with refractory ovarian cancer,[9,10] these drugs have not been shown to have activity in patients who were resistant to the same drugs given intravenously. Cisplatin, in contrast, has produced responses when administered intraperitoneally in patients who were resistant to cisplatin given intravenously. However, the objective response rate, defined as a 50% or greater decrease in solid tumor masses and not merely a decrease in ascites, of intraperitoneal administration of cisplatin in patients with ovarian cancer has not been established. In addition, the vast majority of responses to intraperitoneal chemotherapy have been in patients with nonbulky disease (tumor masses less than 2 cm). The evaluation of intraperitoneal chemotherapy in patients with bulky disease should await the unequivocal documentation of activity in patients with small volume disease.

The clinical situation wherein intraperitoneal chemotherapy with cisplatin warrants immediate evaluation is in patients with ovarian cancer who have small volume residual disease following an induction chemotherapy regimen. The demonstration of clinical activity in this patient population would support further evaluation of intraperitoneal chemotherapy in early stage patients who are at risk for relapse following a surgical procedure and in previously untreated patients in advanced stages. Intraperitoneal chemotherapy may also have a role in preventing relapses in patients who have a negative second-look laparotomy following induction chemotherapy.[11] Until such clinical trials on the efficacy of intraperitoneal chemotherapy are completed, this therapeutic modality should not be considered as standard therapy even though it has been shown pharmacologically to be a success.

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The Stereotype of Organized Medicine

THE STEREOTYPE of organized medicine that seems to be widely held by many opinion leaders, and therefore by many others, should be of concern to medical associations, and no doubt it is. The stereotype is that doctors make too much money, that organized medicine is self-serving and that medical societies, no matter what their rhetoric in behalf of patients or the public, are first and foremost trade associations whose bottom line is protecting and defending the economic and professional self-interests of their physician members. Those who hold and act upon this stereotype include influential persons in government, in the communications media, among the public and probably within the medical profession itself if one thinks of the substantial number of physicians who have not yet chosen to become members of these professional associations or who have discontinued their memberships. On the other hand, public opinion surveys conducted by the American Medical Association and others do not appear to show much public support for this stereotype. Rather, organized medicine is held in relatively high esteem among the general public, and the percentage of the public expressing overall satisfaction with their last visit to a physician was a remarkable 89% in a survey done in 1983. But in no way should the stereotype be lightly dismissed. Legislators, health care policymakers, and leaders of some citizens' groups have spoken out and taken many actions based on their belief in this stereotype which they have accepted as valid.

But just how real is it? How well does the shoe actually fit? It is certainly true that organized medicine does seek to protect the turf of physicians in patient care, it does try to protect physicians' incomes and it does say that this is all done in the interests of good patient care which is surely in the interests of the patients who need this care. However, this is not just rhetoric. Most physicians believe this is true and that by and large what they do in the interests of themselves and their profession results in better care for patients. But organized medicine does other things too. It has a genuine concern with medical education and with the quality, cost and access to care. It is deeply concerned with quality of life for patients and with health and quality of life for all citizens. And it is beginning to find new ways to bring the experience and professional expertise of its members and their professional colleagues to bear on problems of health and health care. The Scientific Board of the California Medical Association and the DATTA project of the American Medical Association may be considered just forerunners of what can and no doubt will be done to bring these great resources of professional expertise and experience more effectively to bear in the patient and public, as well as the professional, interest.

But the stereotype of organized medicine remains, and whatever its validity, it is too often used, and too often unfairly used, against the profession. While it is true that physicians and the organized profession still enjoy substantial public confidence and trust, it is also true that when push comes to shove the real power does not lie with organized medicine. It lies with government, with the communications media, with voters and organizations of voters—that is, with society. It is easy to forget that physicians and the medical profession are given their training by society, and then given the privilege to serve its needs. Confrontation with society is not really an option for organized medicine although at times it has been tried. Rather, both physicians and organized medicine must look to a future of collaboration with patients and with society and put aside the authoritarian past. Just as doctors no longer order patients, the medical profession can no longer dictate to society, but they can and should bring their professional expertise to bear wherever decisions are made that pertain to health care. The current stereotype is something of an albatross around the neck of organized medicine and it will continue to be until the real goals of the medical profession are made more obvious to all.

There are many practical opportunities ahead for physicians and organized medicine to change this stereotype. Competition has already given rise to greater physician concern with a patient's personal convenience. Physicians and organized medicine are moving to fill the vacuum of patient advocacy that has been created by competition, third party and governmental interventions in patient care. The data bases that are coming into being to control costs will provide much needed information on the quality and effectiveness of care which physicians can turn to account to improve quality, costs and access in their own practices. Organized medicine can develop a new emphasis on documented practice performance of individual physicians who are their members. One is reminded that in former times membership in organized medicine was equated with being an "ethical physician" and considered a sign of competence and integrity for practice. Change will come slowly. It will be based upon good performance by physicians and organized medicine, in the genuine patient and public interest, which is understood and appreciated by influential persons in government, in the communications media and among the public.

MSMW

Case Reports

Disseminated *Mycobacterium gordonae* Infection Associated With Glomerulonephritis

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Mycobacterium gordonae is a scotochromogenic mycobacterium that was previously known as the "tap-water bacillus" or *Mycobacterium aquae*.[1,2] It has been commonly identified in human material but is usually considered to be a saprophyte.[1-7] We describe the case of a patient who presented with hypocomplementemic glomerulonephritis as a manifestation of disseminated *M gordonae* infection that was documented by culture of the organism from lung, kidney, urine and cerebrospinal fluid (CSF). The infection appeared to have disseminated from the patient's ventriculoatrial cerebrospinal fluid shunt. Following removal of the shunt and treatment with antituberculous agents, the complement levels and renal function returned to normal. This represents the first reported case of shunt nephritis due to mycobacterial infection.

Report of a Case

The patient, a 23-year-old woman, presented in June 1982 with fever, hematuria and progressive renal insufficiency. A ventriculoperitoneal shunt had been placed in 1973 at the time of surgical removal of a cerebellar medulloblastoma. In 1976 metastasis through the ventriculoperitoneal shunt to the left pelvis was discovered and treated with irradiation plus two years of chemotherapy with vincristine sulfate, methotrexate and lomustine (CCNU). The ventriculoperitoneal shunt was revised several times for relief of obstruction between 1973 and 1981.

In February 1981 fever and night sweats developed several weeks after the patient had four teeth extracted. In March 1981 a ventriculoatrial shunt was inserted because the ventriculoperitoneal shunt had again malfunctioned. Routine CSF cultures were negative but the CSF specimen was not cultured for mycobacteria. Fever was attributed to an *Escherichia coli* urinary tract infection.

(Turner DM, Ramsey PG, Ojemann GA, et al: Disseminated *Mycobacterium gordonae* infection associated with glomerulonephritis. West J Med 1985 Mar; 142:391-393)

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The patient was admitted to hospital in September 1981 for evaluation of intermittent fever that had persisted for six months. A chest x-ray film showed a diffuse interstitial infiltrate without adenopathy. Transbronchial and open lung biopsy specimens showed numerous noncaseating granulomas and acid-fast stains of these specimens were negative. Because of elevated aspartate aminotransferase, lactic dehydrogenase and alkaline phosphatase levels, a liver biopsy was done and the specimen also showed many noncaseating granulomas. An eosinophilic infiltrate was prominent in the liver biopsy specimen. Culture of several blood and urine specimens for bacteria, fungi and mycobacteria were negative. Renal function and the results of a urinalysis were normal. The CSF specimen was not examined for mycobacteria. The patient was discharged receiving prednisone, 60 mg a day, with a presumed diagnosis of hypersensitivity hepatitis and pneumonitis. Within three months the pulmonary infiltrates resolved and her liver function improved. However, when the prednisone dosage was subsequently tapered to 20 mg a day, intermittent fever reappeared. In April 1982 the serum creatinine level was elevated at 1.2 mg per dl and urinalysis showed proteinuria (2+) and hematuria.

In June 1982 the patient was readmitted for evaluation of the fever and increasing renal dysfunction. On physical examination she had a cushingoid appearance, a blood pressure of 155/98 mm of mercury and trace pedal edema. There were no cardiac murmurs or organomegaly. The serum creatinine level was 2.2 mg per dl. Proteinuria, hematuria and erythrocyte casts were found. A 24-hour urine collection contained 1.1 grams of protein. A chest x-ray film, echocardiography and renal ultrasonography showed no abnormalities. Mild stable hydrocephalus was seen on brain computed tomographic scan. Complement levels were decreased and C1q binding was elevated (Table 1). A bone marrow biopsy specimen showed extensive fibrosis with occasional giant cells but no granuloma. Diffuse mild glomerular hypercellularity with subendothelial and mesangial deposits were seen in a renal biopsy specimen. Two of six glomeruli were obsolescent.

Review of the culture results from the previous admission showed that the county health department had reported a 2+ growth of *M gordonae* from the lung biopsy specimen obtained ten months previously. Cerebrospinal fluid aspirated from the ventriculoatrial shunt showed numerous acid-fast bacilli. The cerebrospinal fluid glucose was normal and the protein was slightly elevated. After review of antimicrobial sensitivities of *M gordonae* isolates previously tested at the Centers for Disease Control and at the Cleveland Metropolitan General Hospital, a combination of rifampin, ethambutol hydrochloride and kanamycin sulfate was administered. The ventriculoatrial shunt became obstructed and was temporarily replaced by a ventriculostomy for two weeks before a new ventriculoatrial shunt was placed. After one week of therapy,

TABLE 1.—*Laboratory Findings in a Patient With Disseminated* Mycobacterium gordonae *Infection*

*Date**	*Creatinine (0.5-1.2 mg/dl)†*	*Creatinine Clearance (ml/min)*	*C1q Binding (0-9%)*	*C3 (14-51 mg/dl)*	*C4 (100-200 mg/dl)*	*CH_{50} (80-160 units)*	*Results of Urinalysis*
9/ 8/81	. . .	. . .	. . .	. . .	. . .	. . .	Normal
4/30/82	1.2	. . .	. . .	. . .	. . .	. . .	Protein, erythrocytes
7/ 5/82	1.4	21	60	13	<27	46	Protein, erythrocytes, erythrocyte casts
7/17/82	2.5	12	. . .	. . .	. . .	. . .	. . .
7/23/82	1.7	. . .	11	. . .	. . .	. . .	Protein, erythrocytes
9/22/82	1.4	16	. . .	44	79	77	Protein
10/27/82	1.0	. . .	. . .	43	77	107	Normal
5/15/83	0.9	51	1	36	76	129	Normal

CH_{50} = total complement activity

*Antituberculous drug regimen started on 7/15/82; ventriculoatrial shunt removed 7/17/82 and replaced 7/28/82.

†Normal values and units are given in parentheses.

the fever resolved and the hypertension and renal failure improved by the time of hospital discharge six weeks later. Kanamycin therapy was discontinued because of ototoxicity. *M gordonae* was cultured from specimens of the cerebrospinal fluid, urine, renal biopsy and the ventriculoatrial shunt that had been removed. The identification of the organism was confirmed in the laboratory of Robert C. Good, PhD, at the Centers for Disease Control.

The patient has been maintained as an outpatient on a regimen of rifampin and ethambutol. Renal function has returned to normal (Table 1). Monthly cerebrospinal fluid cultures continued to grow two to three colonies of *M gordonae* until October 1982 but have been sterile since then.

Comments

The mycobacterial infection probably initially developed on the patient's ventriculoperitoneal shunt. The infection then may have contaminated the new ventriculoatrial shunt, with subsequent spread to multiple organs. Specimens obtained from the lung and kidney as well as cerebrospinal fluid, urine and the removed ventriculoatrial shunt all grew *M gordonae*. In addition, sterile saline was used to irrigate the ventriculoatrial shunt at the time of its removal. The undiluted irrigating fluid showed numerous acid-fast organisms by stain. Noncaseating granulomas were found in the liver biopsy specimen although culture of this specimen was negative.

M gordonae is a Runyon group II mycobacterium that is usually found as a soil saprophyte.[1,6] Identification of the organism in humans usually reflects colonization of the oral cavity or respiratory tract without invasive infection. Four previous cases of human infection with *M gordonae* have been reported. The first was similar to that of our patient.[2] Fever, interstitial pneumonia and ascites developed in a hydrocephalic child with a ventriculoatrial shunt after an eight-month history of failure to thrive. *M gordonae* was identified repeatedly in specimens of cerebrospinal fluid and ascitic fluid. Complete clinical remission followed shunt removal and treatment with isoniazid and ethambutol. In a second patient disseminated *M gordonae* infection developed from an infected prosthetic aortic valve.[5] *M gordonae* was identified in specimens from bone marrow, urine and sputum. Clinical remission occurred following valve replacement and administration of isoniazid, ethambutol and rifampin. This patient's infection developed after dental extraction, as possibly occurred in our patient. In a third report,[6] a 50-year-old man with chronic left upper lobe pneumonia had repeated isolation of *M gordonae* from sputum cultures. The infection resolved after 22 months of therapy with ethambutol and rifampin. Recently, there has been an additional report of *M gordonae* infection causing peritonitis in one patient.[7]

There is limited information about antimicrobial susceptibility of saprophytic *M gordonae* strains (Table 2). Sensitivity testing of 24 *M gordonae* isolates by Emanuel Wolinsky, MD, at the Cleveland Metropolitan General Hospital and Dr Robert C. Good at the Centers for Disease Control shows uniform resistance to isoniazid and pyrazinamide. The strains tested are usually sensitive to ethambutol, rifampin and aminoglycosides. Sensitivities of the organisms from our patient and the patient with prosthetic valve endocarditis[5] are similar to those of the saprophytic strains.

Our patient presented with hematuria, proteinuria, erythrocyte casts and renal failure. Mycobacteria may cause renal disease by direct renal invasion, ureteral obstruction or secondary amyloidosis.[8] In 1914 Holten described 15 cases of diffuse glomerulonephritis in autopsies of 2,800 patients with untreated tuberculosis.[9] Membranous and proliferative glomerulonephritis have been observed in renal biopsy specimens of patients with miliary tuberculosis[10,11] and lepromatous leprosy.[12] In our patient the renal biopsy specimen showed neither granuloma nor acid-fast bacteria on smear.

TABLE 2.—*Drug Sensitivity Pattern of* Mycobacterium gordonae

Drug	*Concentration (μg/ml)*	*Organism Isolated From This Patient**		*Other* M. gordonae†	
		Seattle (Percent)	*CDC (Percent)*	*Wolinsky (Percent)*	*CDC (Percent)*
Isoniazid	0.2	58	33	100	100
Isoniazid	1.5	0	33	85	100
Ethambutol hydrochloride	5.0	0	0	8	27
Rifampin	1.0	0	66	15	18
Aminosalicylic acid	2.0	30	. . .	62	27
Kanamycin sulfate	5.0	0	0	. . .	18
Streptomycin	2.0	0	100	70	. . .
Streptomycin	10.0	0	0	23	46
Capreomycin sulfate	10.0	. . .	0	. . .	27
Cycloserine	30.0	. . .	0	. . .	. . .
Pyrazinamide	50.0	. . .	100	. . .	100
Ethionamide	5.0	. . .	100	. . .	100

*Numbers represent percent of resistant colonies of the isolate from this patient found in testing at Harborview Medical Center in Seattle and at the Centers for Disease Control (CDC).

†Numbers represent percent of resistant strains in 13 strains tested by Dr Emanuel Wolinsky[1] and 11 separate strains tested at the CDC.

Glomerulonephritis may occur with bacterial shunt nephritis or bacterial endocarditis. Black and co-workers[13] first described the cases of two patients with nephrotic syndrome in whom control of ventriculoatrial shunt infection was followed by resolution of the glomerulonephritis. Subsequent experience has shown that as many as 27% of cerebrospinal shunts become infected, usually with *Staphylococcus epidermidis*,[14,15] but the incidence of glomerulonephritis in infected patients is less than 5%.[15,16] Hypocomplementemic glomerulonephritis has occurred in patients with chronic, untreated infections as was the case in this patient.[15] The most common clinical manifestations of glomerular involvement are proteinuria and hematuria with nephrotic syndrome present in as many as 29% of cases.[16] The renal lesion most frequently associated with shunt nephritis is a type I membranoproliferative glomerulonephritis with diffuse granular deposition of IgG, IgM and C3.[15-18] Depressed complement levels, elevated C1q binding levels and the finding of bacterial cell wall products in glomeruli have supported an immune complex origin for the glomerulonephritis. In our patient, the presence of erythrocyte casts, elevated C1q binding level and decreased complement levels support a diagnosis of shunt nephritis. Unfortunately, further characterization of the glomerulonephritis by immunofluorescence was not obtained as the biopsy specimen yielded insufficient tissue for immunofluorescent staining.

Replacement of infected shunts has usually been necessary for the resolution of shunt nephritis.[13-20] After shunt removal in our patient, the C1q binding level fell rapidly and complement levels rose. Renal function returned to normal ten months after initiation of antituberculous therapy and replacement of the shunt. At least nine months elapsed between the development of the infection and its diagnosis. This case shows that the diagnosis of shunt nephritis may be missed initially even when infection caused by more common pathogens is sought. Clinical, laboratory and renal pathologic data suggest that this represents a case of shunt nephritis due to mycobacterial infection.

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Somatostatinoma—
The Most Recently Described Pancreatic Islet Cell Tumor

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A 51-YEAR-OLD WOMAN was found with electron microscopy to have metastatic lesions in the liver and immunohistochemical characteristics of somatostatinoma. The concentration of somatostatin in her blood was elevated, as was the calcitonin concentration although calcium, gastrin, adrenocorticotropic hormone (ACTH) and cortisol levels were within normal range. With the establishment of a diagnosis of somatostatinoma, streptozocin was chosen for therapy rather than fluorouracil and doxorubicin, which had previously been administered. We review the 11 previous cases of this tumor, which had been designated as producing the "inhibitory syndrome." With the current availability of specific antisera to entopic and ectopic islet cell hormones and the use of electron microscopy, more such tumors may be recognized. The ultimate goals of such a search are to detect tumors before metastasis has occurred and to indicate the most appropriate chemotherapy.

Report of a Case

In 1978 a 47-year-old woman presented at St. Paul's Hospital (Vancouver, British Columbia) with hypertension. On physical examination no correctable cause was found but hepatomegaly was present. She had no diabetes, her weight had remained unchanged and she had no evidence of malabsorption. She had taken oral contraceptives for eight years. Labo-

(Reynolds C, Pratt R, Chan-Yan C, et al: Somatostatinoma—The most recently described pancreatic islet cell tumor. West J Med 1985 Mar; 142:393-397)

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ABBREVIATIONS USED IN TEXT

ACTH = adrenocorticotropic hormone
5-HIAA = 5-hydroxyindoleacetic acid
VIP = vasoactive intestinal polypeptide
VMA = vanillyl mandelic acid

ratory values included a test positive for infectious mononucleosis and abnormalities on liver function studies. In 1979 persistently abnormal liver function values and a liver scan that showed filling defects led to a liver biopsy. The biopsy specimen showed cellular infiltrates with multiple angiomata. Serum calcium and gastrin levels were normal. A celiac arteriogram showed multiple adenomata. An upper gastrointestinal x-ray series showed external compression of the stomach. No specific therapy was given. In 1980 a second liver biopsy was done at the time of cervical dilatation and uterine curettage. The pathologic diagnosis was angiofibromata.

The following year, diabetes was diagnosed and painful osteoblastic metastatic lesions appeared in the pelvic bones. A regimen of fluorouracil and doxorubicin hydrochloride was initiated. A bone marrow aspirate taken in November 1981 contained malignant cells. A 24-hour test for urinary vanillyl mandelic acid (VMA) gave a value of 4.2 mg (normal, 0 to 7.5); a test for 5-hydroxyindoleacetic acid (5-HIAA) was negative. Repeat tests for serum gastrin and calcium showed no abnormalities. A laparotomy failed to show a primary pancreatic lesion. Computed tomographic scan and ultrasound confirmed extensive hepatic metastasis but no pancreatic tumor was found. In April 1982, electron-microscopic studies of the hepatic metastatic lesions showed intracellular granules characteristic of somatostatinoma; antisera to several islet cell hormones, including insulin and glucagon, gave positive staining for somatostatin only (Figure 1). The patient was not obese and was not taking insulin or oral hypoglycemic agents.

A blood specimen drawn while the patient was fasting, four days after the beginning of a course of streptozocin (750 mg per day for five days), contained 250 femtomol per ml of somatostatin (normal, 120 ± 80 for two standard deviations), 186 pg per ml of calcitonin (normal, 0 to 60) and 48 pg per ml of adrenocorticotropic hormone (ACTH; normal, 50 to 150); serum cortisol was 25.8 μg per dl (normal, 8 to 28), calcium 8.7 mg per dl (normal, 8.6 to 10.3), glucose 151 mg per dl (normal, 65 to 110) and phosphorus 2.4 mg per dl (normal, 2.5 to 4.4). Serum total protein was 5.5 and albumin 3.5 grams per dl; aspartate aminotransferase (formerly, SGOT) 82, lactic dehydrogenase 204 and alkaline phosphatase 579 units per liter (normal, 20 to 90). Prolactin was 24.2 ng per ml (normal, 0 to 20). A sella turcica x-ray series was normal. A brief episode of diarrhea in April 1982 was followed by constipation. No studies were done on the diarrheal fluid as the patient was not in hospital. She has had no symptoms specific for gallbladder disease. When last seen in 1983, the patient was doing well and was experiencing no bone pain. She had been taking streptozocin for four months. Hepatomegaly was decreasing as evaluated clinically.

Laboratory Studies

The bone marrow specimen was fixed in Zenker's fixative and the liver biopsy tissue in formalin for light-microscopic and immunoperoxidase studies. A portion of the liver tissue was recovered from the paraffin block, postfixed in 2% osmic acid and embedded in epoxy resin (Araldite) for electron-microscopy. The hormone content of the tumor was determined by the peroxidase-antiperoxidase technique of Sternberger and associates,[1] using carbozol adapted for measuring somatostatin, insulin, gastrin, glucagon and vasoactive intestinal polypeptide (VIP). The study was done by Anne Worth, MD, of the Cancer Control Agency of British Columbia, Vancouver, BC.

The specimen of the needle liver biopsy done in 1979 showed sheets of small cells with uniform nuclei and scant

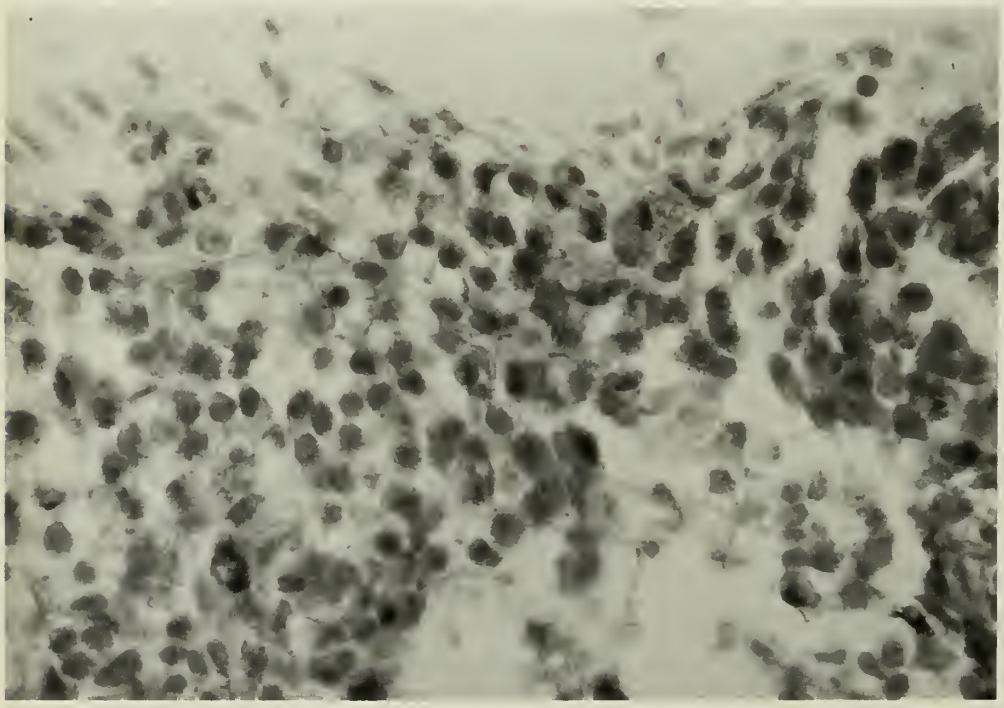

Figure 1.—Immunohistochemical study of the hepatic metastasis showing cytoplasmic somatostatin (see text for method).

cytoplasm separated by large irregular zones of hyalinized fibrous tissue containing calcium deposits. The bone marrow biopsy specimen from November 1981 contained focal peritrabecular metastasis. The tumor had an organoid architecture composed of cells with abundant eosinophilic cytoplasm, uniform small nuclei and no mitotic activity. The trabecular bone abutting the tumor was thickened from pronounced osteoblastic activity. Electron-microscopic studies of the liver biopsy specimen taken in January 1982 showed tumor cells containing small, membrane-limited, uniform, electron-dense granules (200 to 400 nm). Cell ultrastructure, however, was poorly preserved because of formalin fixation. The cell cytoplasm stained strongly with antibody to somatostatin (Figure 1) and was negative for gastrin, glucagon, insulin and VIP by the peroxidase-antiperoxidase technique.

Somatostatin concentration in plasma specimens was measured for us by T. Yamada, MD (Center for Ulcer Research and Education [CURE], Wadsworth VA Medical Center, Los Angeles), using the method of Yamada and co-workers[2] with modification for measuring somatostatin in plasma using antibody 1001.[3] The specimen was stored on ice using aprotinin as a proteolytic inhibitor. Serum prolactin, calcitonin, gastrin and plasma ACTH levels were measured by D. Bednarczyk, PhD, and G. E. Wilkins, MD, at St Paul's Hospital, Vancouver, BC, by standard radioimmunoassay techniques. Urinary VMA and 5-HIAA levels were measured by routine laboratory techniques.

Discussion

Somatostatin is a cyclic tetradecapeptide with a molecular weight of 1,600. It can be found in the hypothalamus, pancreas, stomach, duodenum and jejunum when these organs are studied by specific radioimmunoassay. Specimens of these organs and the thyroid will produce a stain positive for somatostatin by immunohistochemical techniques. The inhibitory activities of somatostatin are widespread and when it is secreted in excessive amounts it produces the "inhibitory syndrome." Although its full physiologic role has not been completely determined, it is known to suppress pituitary release of growth hormone[4] and thyroid-stimulating hormone,[5] pancreatic release of insulin and glucagon,[6] K-cell release of gastrin[7] and intestinal mucosal release of cholecystokinin[8] and secretin.[9,10] Its effects are not confined to the endocrine system, however, as it inhibits secretion of the enzymes amylase, chymotrypsin, trypsin and pepsin[9] and of gastric acid and pancreatic bicarbonate.[7,10]

Within the pancreatic islet somatostatin has a major effect on carbohydrate metabolism via a paracrine influence[11]: the δ-cell produces somatostatin, which inhibits β-cell output of insulin. Insulin from β-cells inhibits the secretion of glucagon in α-cells, whereas glucagon stimulates both insulin and somatostatin production. The blood glucose concentration is a consequence not only of nutrient intake but also of the dynamic equilibrium between the opposing hormones within the islet and at the level of peripheral tissue.

Studies using somatostatin infusion have shown that when it suppresses insulin and glucagon release in normal humans, hyperglycemia may not occur unless glucagon is infused. Gerich and associates[6] found that somatostatin suppression of glucagon release prevented ketoacidosis, yet Lundbaek and colleagues[12] noted that somatostatin suppression of glucagon release did not correct previously established ketoacidosis. Felig and co-workers[13] concluded on the basis of studies with somatostatin infusion that glucagon may worsen the consequences of insulin deficiency but is neither sufficient nor necessary for the development of diabetes.

Significant ketosis can be a finding in patients with somatostatinoma. Axelrod and colleagues[14] found a graded relationship between the plasma somatostatinlike immunoreactivity level and the biologic effects of endogenous somatostatin produced by an islet cell tumor. They concluded that the relationship in humans between the plasma somatostatinlike immunoreactivity level and its biologic effect, such as inhibition of arginine-induced glucagon and growth hormone secretion, is different for different hormones. Furthermore, mild fasting hyperglycemia was present in patients despite inhibition of glucagon release, so that hyperglucagonemia is not required for the occurrence of fasting hyperglycemia, and

TABLE 1.—*Some Clinical and Pathologic Features of Somatostatinoma*

Case	References	Age, Years	Sex	Primary Pancreas	Metastasis in: Liver	Bone	Other	Gallbladder Disease	Diabetes	Anemia	Hypertension	Diarrhea or Steatorrhea	Other Hormone Excess	Survival
1. . .	Larsson et al, 1977[15]	55	♀	+	+	−	. .	+	+	−	NS	+	. .	Few hours post-operatively
2. . .	Ganda et al, 1977[16]	46	♀	+	−	−	. .	+	+	+	−	−	. .	4 years (SA)
3. . .	Kovacs et al, 1977[17]	54	♂	+	+	−	. .	NS	+	NS	+	−	ACTH	6 days post-operatively
4. . .	Pipeleers et al, 1979[18]	63	♀	+	+	−	. .	+	+	+	NS	+	. .	30 weeks (SA)
5. . .	Kjejs et al, 1979[19]	52	♂	+	+	−	. .	+	+	+	−	+	Calcitonin	10 months (SA)
6. . .	Penman et al, 1980[20]	33	♀	+	+	−	Nodes	−	*	NS	NS	NS	Insulin	NS
7. . .	Penman et al, 1980[20]	36	♂	+	−	−	. .	−	+	NS	NS	NS	ACTH	2 years (SA)
8. . .	Galmiche et al, 1980[21]	70		+	+	−	Duodenum	+	+	−	−	+	Calcitonin	4 weeks post-operatively
9. . .	Bloom and Polak, 1980[22]	NS	NS	+	−	−	. .	NS	+	NS	NS	+	. .	. .
10. . .	Asa et al, 1980[23]	68	♀	+	+	−	Nodes	NS	+	+	−	+	Endorphin, Calcitonin, ACTH, gastrin	20 months
11. . .	Axelrod, 1981[14]	54	♀	+	+	+	Kidney, adrenal, thyroid, skin, ovary	+	+	+	−	+	. .	15 months
12. . .	Reynolds et al, 1985	51	♀	?	+	+	. .	−	+	+	+	+	Calcitonin, PRL ±	5 months (SA)

+=yes, −=no, NS=not stated, SA=still alive at time of report, ACTH=adrenocorticotrophic hormone, PRL=prolactin

*Patient had hypoglycemia.

significant ketosis can occur. When our patient was fasting, the serum glucose value was in the range of 140 to 170 mg per dl and there was no evidence of ketosis. She was not obese. Unfortunately, plasma insulin and glucagon levels were not measured due to a technical problem. We assume that the elevated level of circulating somatostatin caused suppression of insulin and glucagon release, a phenomenon that has been shown repeatedly by others.

Somatostatinomas are apparently extremely rare, only 11 cases having been reported.[14-23] In Table 1 the major clinical and pathologic features of these cases and of our own are set forth. The case of deNutte and co-workers[24] seems to be the same as that of Pipeleers and colleagues,[18] and that of Wright and associates[25] is included in the report of Penman and colleagues.[20] Pancreatic islet cell tumors can be divided into those that produce entopic hormones and those that produce ectopic hormones.[26] The first category includes the insulinoma (hypoglycemia syndrome),[27] glucagonoma (diabetes-dermatitis syndrome),[28] somatostatinoma (inhibitory syndrome), pancreatic polypeptidoma (no characteristic syndrome but pancreatic polypeptide serves as a marker for diarrheogenic and ulcerogenic syndromes)[29] and the very complex carcinoid islet-cell tumor (atypical carcinoid syndrome).[30] The second category includes the pancreatic gastrinoma (ectopic ulcerogenic syndrome),[31] vasoactive intestinal polypeptidoma (watery diarrhea-hypokalemia-achlorhydria syndrome of Verner and Morrison),[32] corticotropinoma (ectopic ACTH syndrome),[33] parathyrinoma (ectopic hypercalcemia syndrome),[34] vasopressinoma (ectopic syndrome of inappropriate antidiuretic hormone)[29] and ectopic cholecystokininoma (syndrome of diarrhea with excess gastric acid but without ulceration).[35] The presence of hypertension in one previous case and in the current case may be coincidental, considering the prevalence of hypertension in the general population.

The simple concept of one hormone of tumorous origin giving rise to one clinical or biochemical problem must give way to new ideas: a pancreatic tumor can secrete many hormones, leading to many problems; it can elaborate a single hormone creating many problems, and the pattern of hormone secretion and the biologic response to those hormones can change with time. Of the 11 somatostatinoma cases in the literature, gallbadder dysfunction (representing inhibition of cholecystokinin) was present in six, steatorrhea or diarrhea in seven, diabetes (representing inhibition of insulin release) in ten and hypochlorhydria (representing inhibition of gastrin) in three. In association with hypersomatostatinemia, three patients have had elevated ACTH levels,[17,20,23] one had hyperinsulinemia causing hypoglycemia,[20] four (including our own) had hypercalcitoninemia,[19,21,23] and one had elevated calcitonin, ACTH, gastrin and α-endorphin levels.[23] The mechanism by which anemia has occurred in some cases is uncertain, although it may be via erythropoietic suppression. Because of the presence of M-protein and metastatic lesions to bone, one case was diagnosed and treated as multiple myeloma before the correct diagnosis was reached.[14] The mild elevation of the prolactin level in our case may or may not be significant. No conclusion can be drawn as only one measurement was done, and that measurement can be considered normal for the luteal phase of the menstrual cycle.

In our case, the primary site has not yet been identified, but in all of the previous cases, the primary was a single pancreatic lesion ranging in size from 0.5 to 20 cm. We did not do a pancreatic arteriogram or get a transhepatic portal venous hormone specimen. Hepatic metastasis had occurred in 9 of the previous 11 cases, as well as in ours. Our case is the second with bone metastasis but the first to be reported with osteoblastic, rather than osteolytic, lesions.[14] Some cases were discovered at the time of a cholecystectomy. Our patient presented with hepatomegaly, abnormal findings of liver function tests and filling defects on the liver scan. Initially, therapy was started with a regimen of fluorouracil and doxorubicin but when the diagnosis of pancreatic endocrine tumor was established it was changed to streptozocin. Previous cases have been treated by radical pancreatoduodenectomy,[13,14,20] enucleation[19] or by biopsy and streptozocin therapy.[14,19] One patient's disease had infiltrated to the pancreas with metastasis to liver and peritoneal lymph nodes, so only biopsy was done. Treatment postoperatively was with benzothiadiazine and fluorouracil.[19]

It is unclear what combination of features should lead to a concerted effort to find somatostatinomas. With the widespread availability of localization techniques such as ultrasonography, computed tomography and arteriography, more such cases should be uncovered, provided that a physician applies these tests appropriately, even in cases of metastatic lesions. The presence of associated problems such as diabetes, diarrhea, anemia and cholecystic disease should be reason to pursue the diagnosis of a rare endocrine tumor. The ultimate goals of such a search would be to detect and classify the tumor at the earliest possible stage and to indicate the most appropriate chemotherapy.

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Accidental Dopamine in the Eye

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WE IN THE MEDICAL profession are frequently made aware of unusual and often unexpected side effects of commonly used drugs. These effects may appear either when the drug has been given in the usual manner or when the recommended dosage has been inadvertently exceeded. Occasionally an unanticipated reaction may arise when a drug is instilled via an unintended route. This may occur through the mucous membranes of the eye, which are capable of systemic drug absorption, as confirmed by recent reports of cardiovascular sequelae related to the use of pindolol, metoprolol and epinephrine eye drops.[1-3] In a review of reported systemic side effects of ophthalmic drugs in common usage before 1977, the use of at least one drug, phenylephrine, was found to be associated with several instances of serious untoward effects.[4] Persons working in chemical plants and laboratories know that the eyes are important areas for accidental drug contamination. I report a case of accidental instillation of dopamine in the eye of an intensive care unit nurse.

Report of a Case

A healthy 32-year-old woman, an intensive care unit nurse, accidentally splashed one or two drops of undiluted dopamine into her left eye while preparing a standard dilution for intravenous use. She dried the eye and continued to work until several minutes later when she noted the abrupt onset of dizziness, palpitations, facial flushing and a dry mouth. She went to the emergency room, where an electrocardiogram showed supraventricular tachycardia at a rate of 160 per minute with diffuse nonspecific ST-T abnormalities (Figure 1.) She was admitted to hospital for observation.

(Strauss R: Accidental dopamine in the eye. West J Med 1985 Mar; 142:397-398)

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Her medical history included mild hypertension of one year's duration, well controlled on a regimen of amiloride (5 mg) and hydrochlorothiazide (50 mg) every other day. She said she had no history of cardiac disease, rheumatic fever, heart murmur, chest pain, palpitations or dizziness and was receiving no other medications.

Findings of a physical examination were remarkable only for a pulse of 160 and a blood pressure of 152/100 mm of mercury. A cardiac examination done during periods of sinus rhythm showed no abnormalities. Laboratory results included normal values for blood count, electrolytes and free thyroxine. A standard M-mode echocardiogram was normal.

The patient's hospital course was characterized by spontaneously resolving periods of paroxysmal supraventricular tachycardia and intermittent sinus tachycardia, which gradually became less frequent. She was able to identify these as periods of flushing and palpitations. The episodes of tachycardia were not responsive to carotid sinus massage, but did revert on one occasion after she was given verapamil, 5 mg, intravenously. On the following day, an electrocardiogram was within normal limits (Figure 2). Except for fatigue and a fair amount of anxiety over the mishap, she was discharged in good condition on the third hospital day. Values for serum catecholamine and urine metanephrine obtained after her discharge were within normal limits.

Discussion

This case is a dramatic example of a seemingly innocuous amount of conjunctival contamination causing significant morbidity. It we estimate that there are ten drops per milliliter, one drop of undiluted dopamine (40 mg per ml) contains a dose of 4,000 μg. Assuming that only one drop contaminated the eye of this 65-kg woman, she received an approximate bolus of 60 μg per kg, not an inconsequential amount! There is little doubt that there was a direct causal relationship between the mishap and the ensuing events. Dopamine has well-known β-mimetic effects that could have been responsible for the tachycardia experienced by this woman.[5] When dopamine is given intravenously, its effect is gone within minutes. It was surprising to us that episodes of paroxysmal tachycardia continued for as long as 48 hours. This led us to exclude the possibility of underlying thyrotoxicosis, pheo-

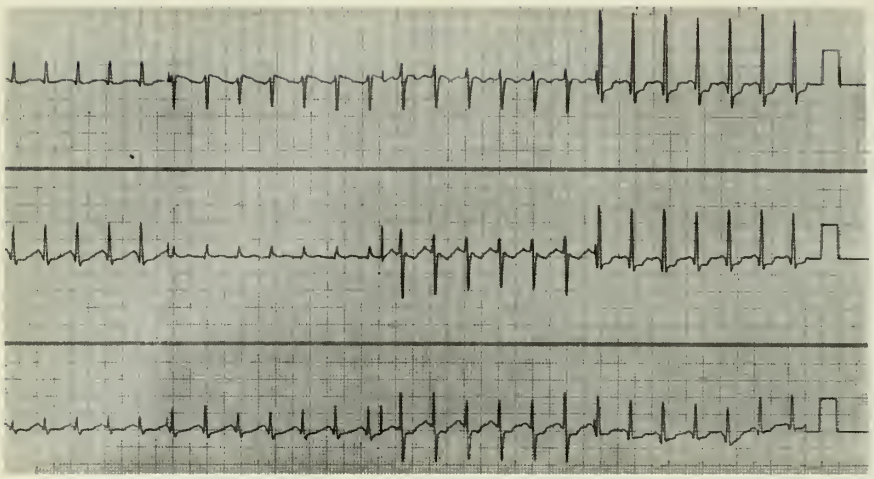

Figure 1.—Initial electrocardiogram.

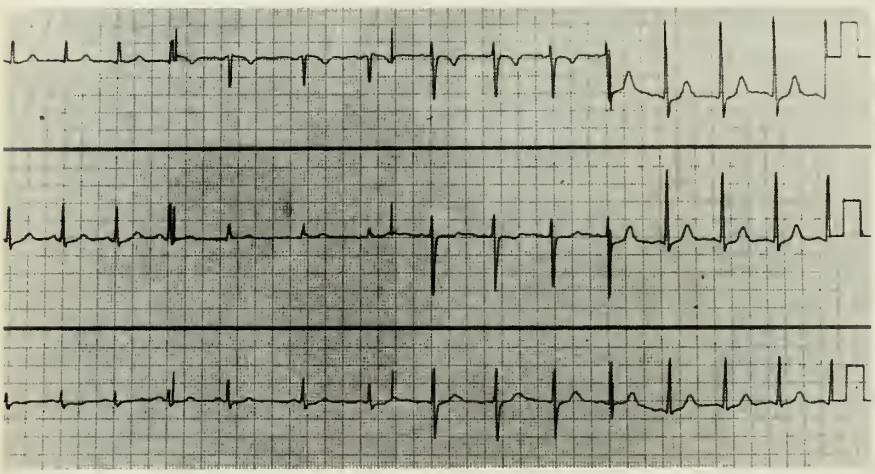

Figure 2.—Electrocardiogram done on second hospital day.

chromocytoma or cardiac disease. One possible cause of the prolonged effect is that there is a drug reservoir at the conjunctival membranes. Another possibility is that the considerable anxiety caused by the initial episode led to further episodes of tachycardia. This seems unlikely as a sole explanation, as the patient experienced some episodes during sleep.

The lessons from this case are several. First, persons in a hospital setting responsible for handling potent pharmacologic medications need to be reminded of the possibility that large-dose contamination can occur when seemingly small amounts of a drug are spilled on mucous membranes. Second, prompt irrigation or other appropriate measures should immediately be done if such an accident does occur.

A more interesting implication is the possible role of mucous membranes in drug administration. One intriguing and potentially useful technique might be the instillation of cardiac drugs through the mucous membranes of patients during cardiopulmonary resuscitation or other emergent situations before intravenous access can be established. Certainly the nasal mucosa and the underside of the lip and tongue are well-established routes for drugs; might not the eye provide yet another alternative?

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Correspondence

The Editorial Board will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words, and must be typewritten, double-spaced and submitted in duplicate (the original typescript and one copy). Authors will be given an opportunity to review any substantial editing or abridgement before publication.

Ischemic Bowel Infarction and Phenylpropanolamine Use

TO THE EDITOR: Phenylpropanolamine (PPA), a sympathomimetic structural analogue of amphetamine, has been the subject of several recent reports citing amphetamine-like adverse side effects. Temporal association of ischemic effects involving the coronary,[1] renal[2] and cerebral[3] vasculature has been previously reported. To our knowledge, compromise of the visceral vascular bed has not been described.

Report of a Case

A 45-year-old woman presented to our emergency room with a 24-hour history of progressive crampy abdominal pain and bloody diarrhea. The pain had initially been ill-defined and periumbilical but had more recently become well localized to the right lower quadrant and had become increasingly severe. The patient had been in excellent health before the onset of her pain, and her medical history was remarkable only for an appendectomy as a child. Specifically, there was no history of cardiac, rheumatologic or atherosclerotic vascular disease. She was not taking oral contraceptives but had been regularly using a proprietary diet aid, Dexatrim (65 mg of phenylpropanolamine hydrochloride per capsule), for three years. Her initial dosage was low, one to two capsules a day, but she had increased the dosage to three to four capsules per day over the two months before admission in an effort to increase weight loss for her upcoming wedding. At this time, her weight was 60 kg and her height 157 cm.

On presentation, the patient appeared acutely ill. She was febrile and dehydrated. On physical examination, hypoactive bowel sounds and moderate abdominal tenderness that was maximal in the right lower quadrant were noted. There was grossly bloody stool in her rectum; proctoscopic examination showed normal-appearing rectal mucosa with blood from above 25 cm.

Findings on cardiovascular and dermatologic examinations were normal. Abdominal x-ray studies showed an ileus pattern with air-fluid in the left upper quadrant. An x-ray study of the chest and an electrocardiogram showed no abnormalities. Findings on a complete blood count were notable for a leukocyte count of 18,000 per μl with a left shift. Results of SMA-6 and urinalysis were within normal limits.

Over the 12 hours following admission and initial resuscitation, the patient became hemodynamically unstable and peritonitis developed. She then underwent emergent exploratory laparotomy. Operative findings included dark, foul-smelling peritoneal fluid and an obviously ischemic proximal colon with necrosis of a segment of midtransverse colon. There was no gross evidence of either arterial or venous obstruction. An extended right colectomy was carried out with an ileostomy and transverse colon mucous fistula. Gross examination of the resected specimen showed mucosal necrosis. Histopathology was consistent with ischemic colitis, and there was no histopathological evidence for a vasculitic or atherosclerotic etiology for the ischemia.

The patient was advised to refrain from further use of diet pills. One year later she underwent ileocolonic reanastomosis without complication. She has continued to do well without recurrent abdominal complaints.

The cause of the colonic ischemia in our patient is uncertain. There is no evidence of embolic or thrombotic disease, and other reported causes (oral contraceptives, vasculitis, amyloidosis) were not present. As a structural analogue of amphetamine, PPA may have had a role in the ischemic bowel infarction in our patient. Methamphetamine abuse has been shown experimentally to lead to fibrinoid necrosis in intracerebral vessels with the formation of microaneurysms. The mechanism for these vascular changes is thought to be a necrotizing angiitis that is indistinguishable from periarteritis nodosa.[4] This may also involve renal as well as other visceral arteries. Radiologic evidence of cerebral vascular spasm has been reported in one animal study where amphetamines were injected through carotid vascular catheters.[5] Although we cannot document a definite causal relationship between PPA and the colitis seen in our patient, the temporal relationship is suggestive.

Phenylpropanolamine products are widely used in decongestants, anorexiants and "legal stimulants." With the increasing use of this drug, the list of adverse reactions appears to be correspondingly lengthening. The knowledge that a patient has used this drug may be of historical importance in evaluating otherwise unexplained ischemic visceral events.*

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Munchausen Alert

To the Editor: One opportunity to contain rising hospital costs is in early recognition of the "hospital hobo" or Munchausen patient. To remind and alert physicians, we describe a case admitted to Pacific Presbyterian Medical Center, San Francisco, on October 15, 1984.

A 29-year-old, obese white woman walked into the emergency room with the chief complaint of her jaw "going out to the right" while drinking a carbonated beverage. Her jaw had been fractured, she reported, one year before in a fight with a girlfriend. She stated that on her way to our hospital she suffered a seizure, witnessed by friends, and was afraid that her jaw was fractured again. In addition, her surgeons last year (she could not say who or where) elected to stabilize the fragments with rubber bands instead of conventional wires, so she expressed concern that the jaw had not healed properly. She told the emergency physician that her seizures began at age 15 after a head trauma from a fall in gym class. Her current medications were carbamazepine (Tegretol), 200 mg three times a day, and valproic acid (Depakene), 250 mg three times a day.

While having mandible x-ray films made, the patient had another seizure, witnessed by a technician, who considered it to be grand mal epilepsy. She was then sent to the intensive care unit. There she told physicians that she last saw her local neurologist a month ago; she was in San Francisco for a vacation. Past complications included eight respiratory arrests during seizures and two cardiac arrests when phenytoin (Dilantin) was given by rapid intravenous push. Allergies included penicillin, aspirin, codeine, diazepam (Valium) and tetanus toxoid. Her father had seizures, also due to a head trauma, and her daughter died at five months of age due to respiratory arrest from febrile seizures. Her occupation was that of a truck loader. Finally, she had also had two exploratory laparotomies after motor vehicle accidents (the last in May 1984), several venous cutdowns, a cesarean section, a ganglion cyst removal and mild asthma.

Physical examination on admission revealed anisocoria (the right pupil 1 mm greater than the left), a small parietal hematoma and tenderness of the left temporomandibular joint. Neurological examination was significant only for weakness in the right hand and forearm, allegedly due to "nerve damage" from the cutdowns. Her left ankle was in a cast, reportedly placed after a fracture. Her general hygiene was poor, especially dental hygiene, and many teeth were missing.

The patient continued to have seizures throughout the night. Her nurse recorded seizures after a monitor alarm went off, after having foot pain and after being touched on the hand. There was also a seizure after the bedside light was turned on, at which time she stated that her seizures were easily triggered by bright lights and loud noises. Between such episodes, she smoked cigarettes and drank liquids through a convenient aperture in the teeth on the right side of her mouth.

We first saw her about 12 hours after admission. Knowing the valproate level was only 8.4 μg per ml (the therapeutic range 50 to 100), we asked if she had been taking her medication. Through clenched teeth and a jaw jutted to the right, she spoke with little difficulty, telling us that the drugs were taken faithfully. Her neurologists wanted to keep her levels subtherapeutic because she became ill very easily. Use of several other medications in the past had not been successful, including phenobarbital, she said. Yet, before her second motor vehicle accident (May 1984) she only had seizures every two to three months. After the accident they increased to every other day. In addition, she was unconscious for two days after the accident and later, because of severe abdominal pain, underwent an exploratory laparotomy which revealed "three ruptured ovarian cysts." A computed tomographic scan of her head was normal. She then remembered having had two additional seizures while in the ambulance coming to the hospital, but it was noted that she had actually walked in alone.

On our physical examination, palpation of the temporomandibular joints caused no pain when she was distracted. Among her abdominal surgical scars, there was one with a fresh excoriation due to a "stitch abscess." While checking her pupillary response to light, however, she started to blink and stare off to the right. This was followed by tonic-clonic movements of the arms and head. After the seizure, she was unarousable, but returned to her previous state within four minutes. An electroencephalogram was obtained an hour later. It showed no seizure activity, nor any sign of postictal depression, although some mild abnormalities were noted.

That night, the patient signed out against medical advice. The intensive care unit staff had tried to verify, but could not, the existence of her neurologist in central California. When requestioned about this person, she had become furious. It had also been determined by the surgical consultation and x-ray studies that the jaw was not dislocated. We felt that she had been deliberately deviating the mandible. In addition, phenobarbital, which she had denied taking at present, was detected in blood specimens.

With the many inconsistencies in this case, we could only conclude that the patient suffered from Munchausen's syndrome. No doubt other hospital staff will see her in the future. We can supply further details upon request.

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Thrombosis of the Iliac Artery From Seat Belt Injury

To the Editor: The use of seat belt restraining systems in motor vehicles can protect occupants from major and fatal injuries. Studies have shown a 60% decrease in injuries and a 35% reduction in fatalities by the use of restraining devices.[1,2] An injury caused by a safety belt was first reported by Kulowski and Rost in 1956.[3] This case illustrates a vascular injury incurred from seat belt wear.

Figure 1.—An injury to the left common iliac artery is shown, adjacent to the origin of the internal iliac artery.

Report of a Case

A 42-year-old man, previously healthy, was a front seat passenger in an automobile that was struck from behind by a vehicle moving at high speed. The automobile was projected forward and ran into a wall. The patient had been restrained by a lap-type seat belt and was able to walk away from the accident without apparent injury. However, the next day he began to experience pain and paresthesias in his left leg extending from his buttock to his foot, with ambulation making the pain more severe.

Physical examination showed diminished pulses in his left femoral, popliteal and dorsalis pedis arteries. The left ankle pressure was 86 mm of mercury compared with 154 mm of mercury on the right. Arteriography showed an injury to the left common iliac artery adjacent to the origin of the internal iliac artery (Figure 1). The right iliac system and bilateral distal vessels were normal.

In surgery the common and external iliac arteries were found to have a posterior atherosclerotic plaque. An area of thrombus occluding the vessel lumen was identified at a disruption of the plaque near the bifurcation of the common iliac artery. Thrombectomy and angioplasty were carried out. Postoperatively the patient became symptom free with a left ankle pressure of 140 mm of mercury.

Discussion

There can be no doubt that passenger restraining systems in automobiles are effective safety devices.[1,2] Nevertheless, physicians must be aware that seat belts can occasionally be the cause of injury. A number of intestinal and spinal injuries have been reported[4] but vascular injuries caused by seat belts are rare. Before this case only five cases had been reported.[4,5] A common denominator with these cases and the one presented here is the presence of preexisting atherosclerosis.

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Baby Fae

To the Editor: On October 26, 1984, a 15-day-old infant known only as Baby Fae received the heart of a 7-month-old female baboon. And on November 15, two weeks later, Baby Fae was dead. The autopsy revealed rejection of the baboon heart and renal failure. Baby Fae was born with a congenital anomaly known as the hypoplastic left-heart syndrome. With this malformation the left ventricle and the aortic arch are only partially developed and the infant usually dies within days or weeks after birth.

This cross-species transplant was a medical first. Baby Fae was the longest surviving human recipient with an animal heart. Heretofore, only three other simian to human heart transplants have been performed, and all were in adults. Two of the recipients died within hours of the transplantation. The third, Benjamin Fortes, survived three and a half days after receiving a chimpanzee heart.

Baby Fae's history-making surgery was done at Loma Linda University Medical Center in California and the surgical team was headed up by Dr Leonard L. Bailey. The research team plans to perform four more baboon to infant transplants in the current research program, according to reports circulated. In the last six years Dr Bailey has performed over 150 cross-species transplants on young goats and sheep. Indeed, it would appear that Dr Bailey's extensive experience with these interspecies transplant experiments between goats and sheep were designed to lead up to the extraordinary leap—a baboon to human transplant. Apparently the medical community was taken by surprise when the news of the baboon to human transplantation was released. No federal money or grants from agencies outside of Loma Linda Medical Center were involved in the research, and therefore no outside accountability was required. Perhaps this explains why the medical community was taken by surprise. According to reports Dr Bailey did publish several papers dealing with the animal studies but they were not enough to alert his peers that the animal work was leading up to a human operation. Baby Fae, like all infants, had an immature immune system. The anticipated rejection phenomenon was expected to be less pronounced in Baby Fae, and it was the hope of the research team that this would enhance her chances of survival. In addition, cyclosporine was expected to suppress the baby's propensity to reject a transplanted organ from another species. This drug has substantially improved the success rate of human organ transplantation surgery. Clearly, the Baby Fae case is on the cutting edge and the learning edge of medical research. The medical frontier has been pushed forward considerably.

But the medical, ethical and legal questions and issues raised by this novel human experiment are many: Were there any medical alternatives to the cross-species transplant? Was the family fully apprised of these alternatives (human organ transplantation and corrective open heart surgery)? If these alternatives were not fully disclosed with the family did they really give a proper informed consent? What role did the

Loma Linda Ethics Committee play in this historic event? Was the Committee apprised of the availability of human hearts before approving the human experiment? Did the Medical Center's Institutional Review Board carefully and thoroughly go over all the alternative forms of treatment with the family before granting their approval? It is the responsibility of the Institutional Review Board to make certain that the family is given full disclosure. Indeed, the Institutional Review Board had the task of protecting the rights of Baby Fae and the responsibility of educating the family relative to the doctrine of informed consent. Did the surgical team make an effort to get a human heart? Or did they bypass this route since they were committed to an animal-heart transplant? Was the infant made the object of research when a more traditional approach was possible? Is this an example of medical sensationalism at the expense of the baby and her family?

We are in an age of personal autonomy, self-determination and individual freedom in connection with patients' rights. Accordingly the doctrine of informed consent has become a major legal issue in medical practice in the United States. The ethical and legal imperative is the duty of full disclosure. But the duty of disclosure varies with the medical circumstances. As one goes from an emergency situation to an elective medical event the burden and duty of disclosure increase. In the case of human experimentation, informed consent takes on far greater legal weight and significance. Moreover, thorough informed consent is the cornerstone of any human experimentation program. One of the major responsibilities and functions of the Institutional Review Board is to make certain that the patient or, in the case of a minor, the patient's family can give a proper informed consent. Complete and full disclosure is the standard. All information that would allow a reasonable person to make prudent choices should be disclosed. Perhaps this was done in the Baby Fae case. We don't know since Loma Linda Medical Center has not released the consent form used in this case.

The ethical and legal imperative dictates that the physician provide sufficient information about the patient's condition and recommend a course of action. And all benefits, risks, complications and alternatives associated with the proposed treatment are to be disclosed. Thus, the patient—or in this case the family—is expected to make a responsible and informed decision either to accept or reject the recommended form of treatment.

The controversy over Baby Fae probably will continue for some time. In the meantime the frontiers of medicine have been advanced by this experiment. And, philosophers, ethicists, theologians and physicians will argue the pros and cons of this event. But one thing is certain: Although what we know in medicine is dwarfed by what we don't know, we now know a little more.

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Hygienic Management of Hypertension

TO THE EDITOR: Kudos for publishing the excellent article by Dr G. N. Aagaard on treating hypertension.[1]

The author speaks of "hygienic" treatment as being more desirable than drug therapy in mild hypertension; I agree.[2-7] But it can also work in more severe cases.

Coffee, tobacco, sugars, salt and alcohol are all known to increase blood pressure. Starting by proscribing these, my hygienic therapy moves on to the following: (1) Eating foods "as grown" or close to "as grown." (2) Eating what one can "take or leave alone," not what one loves or craves. (3) Including generous amounts of raw salads and seeds in one's eating plan.

When provided with these simple hygienic measures, many of my hypertensive patients improve greatly. For example, a 57-year-old woman on a regimen of drug therapy for 19 years said, "I would consider it a miracle to be able to control my blood pressure without drugs."

When she was taking a diuretic and alpha-methyldopa, her blood pressure at first visit was 160/95 mm of mercury. Six weeks later, after the patient adopted the above life-style changes, it was 130/70 without medication.

Life-style therapy, especially eating-style therapy, is a potent antihypertensive therapeutic modality. But, though this general method has worked for many patients, I had a case that was unusually difficult. Professor Norman Kaplan, MD, from Northwestern, suggested I describe it for the medical literature.

Report of a Case

A reasonably slender 37-year-old woman asked on her first "health improvement service" visit if she could control her newly diagnosed hypertension with life-style changes. I told her I thought she could. After two years her blood pressure was 170/95 to 190/110 mm of mercury on a regimen of propranolol hydrochloride, 40 mg twice a day, and alpha-methyldopa, 250 mg three times a day. She could not tolerate diuretics, becoming severely hypokalemic despite five to six tablespoons of 10% potassium chlorate per day. Endocrinological workup and hypertensive workup were negative.

Despite staying thin, avoiding salt, keeping her food and activity diary and being exceedingly compliant, she was no better off than when she came for her first visit. I then had her test certain foods with the four-days-off, one-day-on challenge protocol. She reacted to wheat and yeast. Although she loved bread, she stopped eating wheat and yeast. Her blood pressure was 130/80 mm of mercury in ten weeks, off all medicines. (One slice of bread would raise her diastolic blood pressure 20 to 30 mm of mercury.)

Experience suggests, therefore, that certain items (such as salt, cholesterol, coffee, tobacco, alcohol, animal fat and low-fiber food) may *generally* raise blood pressure and others (wheat and yeast, for example) may *specifically* raise it.

Hygienic management of hypertension seems to be useful and especially so when done scientifically. This includes keeping a food diary, using a general elimination diet and following a challenge protocol when necessary.

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A Protective Helmet for Infants and Children Who Accompany Their Parents on Bicycles

To the Editor: Approximately 1 million injuries a year are estimated to result from bicycle accidents,[1] yet the number may be higher since most bicycle injuries go unreported. More than 78% of bicycle-related fatalities occurring during 1973 involved children.[2] Bicycle accidents constituted the single largest cause of head injuries in patients admitted to Children's Hospital of Eastern Ontario.[3] A third of all bicycle-related injuries are above the neck.[4] A helmet that can protect the skull has then an 11% capability of reducing injuries.[5]

In an effort to decrease the incidence of head injury in infants and young children, the Division of Neurosurgery and the Department of Pediatrics of the University of California, San Diego, carried out a field study with protective helmets in infants.

A design system of two helmets was employed (provided by Bell Helmet, Inc, Norwalk, Calif). The lighter helmet was used for the infants. Restraining straps to hold the helmet in place were easy to apply, but difficult for the child to remove. To adapt the helmet and fit it properly to each individual infant, additional Styrofoam pads were available. The construction of the helmet, together with the design, was directed to meet the modified standard of the American National Standards Institute (Z-90.4).[6] For the development of the helmet, the performance of various prototype configurations was tested, utilizing the modified American National Standard Institute, Inc,[7] for impact attenuation. The helmet was made of a material that would satisfy this test and also be light enough to be tolerated by an infant or toddler, without undue upright balance difficulty or weight of the head, that would cause strain to the cervical spine. For that purpose, a polystyrene shell with urethane coating was employed. The final weight with coating was 240 grams for the infant helmet and 300 grams for the toddler.

There were very few complaints or observations from the parents in the population of infants and toddlers studied (see Table 1). Four children were noted by the parents to struggle for several minutes when the helmet was first placed in the initial periods of helmet usage. When they realized that they were unable to remove them because of the strap design, they finally accepted the helmets for the duration of the bicycle rides. There were no complaints of limitation of movement of neck or head discomfort by the parents or the children; there did not seem to be any visual difficulty in the infants. It must be noted that the usage period was variable, but usually short.

In children within the one to five year age range, accidents are the most common cause of death; 30% of the deaths are secondary to head injury, and approximately 75% of all pediatric hospital admissions for trauma are because of injury to the head.[8] Though the incidence of admission to hospital because of a head injury has increased over the past years in the pediatric age group, little has been done about prevention. Since more than a third of all injuries from bicycle accidents are above the neck,[4] it is felt to be most important to protect the cranium with a helmet. However, though multiple helmet systems are available for the adolescent and adults, there are fewer systems available for the younger child, and the helmet presented here seems to fulfill these requirements.

TABLE 1.—*Study of Protective Helmets in Infants and Toddlers*

Number of children	15
Age range	8-44 months
Mean age	23.4±12.7 (SD) months
Duration of helmet use	69.2±54.1 minutes

SD=standard deviation

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Data on Medical Costs

To the Editor: There are times when it is tempting to label as a contagion the closed mind practice of data collection and interpretation that is found in the ever increasing reports and comments on medical care costs. To be sure, the current perception continues to lack the greater sophistication that you had once counseled in an editorial.[1] What we continue to see in the pool of data is a one-sided economic evaluation of medical services which treats the money spent for medical services as if it were a total loss ("consumption") and neglects, or is unaware of, the valuable benefits flowing from the diffusion of such money into the general economy. Thus, the common thread of transfer of purchasing power in market transactions, adding wholeness to the concept of exchange, is absent.

Those who subscribe to the notion that the gross national product (GNP) measures national product need gentle prodding by pointing out that the Bureau of Economic Analysis (Commerce Department) measures national product "by adding up what everyone spends."[2] The money spent for medical services is part of the total spent nationally. The market component of the medical care enterprise produces the portion of the GNP that it is supposed to "consume." Remove what it "produces" (spends) and the GNP is diminished; it does not allow more resources for spending. Of course, what

is basically involved is that we are urged to spend less for medical care. Here, the question of values versus costs enters and properly so only in limited instances. Nevertheless, the myth of "consumption" and of a "statistical portion of the GNP" persists *only* in medical care spending. (Parenthetically, it might be added that there are grounds for the statement that the public sector itself, not the private, often "consumes" our resources.)

You have also raised (in the previously cited editorial) the need for "much public and professional education" with regard to medical costs. In this turbulent shake-up period, when the community of economists stretch thin their concepts to somehow find a proper niche for the professed industrialization of medical care, we do need a firm foundation of valid data to counter some of their groping.

The work of Dr David A. Rothstein[3] of the University of Chicago—beginning in 1975—provides such a foundation. His basic tenet, adapted to medical care services, is that "one sector's (person's) expenditure is another sector's (person's) income. Or, one sector's output becomes an input to others ("input-output model").

The original framework of an input-output model of industries with its economic application was developed by Professor Wassily Leontief in 1936, with subsequent studies published between 1944 and 1974. This work earned him the Nobel Prize in economics in 1973. Leontief is the principal investigator in a study currently being done at New York University to extend Rothstein's observations of the role of an input-output model in medical care expenditures. The idea was also incorporated into an ongoing study at Harvard. Perhaps the important economic role of medical care spending will become more widely recognized.*

Such interest in the positive economic benefits of money spent on medical services is, of course, not new. A few years ago, Dr William Barclay,[4] then Editor of *JAMA*, wrote a brief recital of the economics of medical services showing a penetrating insight into the input-output interdependence of medical care spending. The enduring silence that followed his editorial raises some concern about its motivation. Not that Dr Barclay was opposed to reminders of cost. What he opted for was "one more element in the data base from which a physician draws in making decisions." But not one that, as currently practiced, supersedes all other considerations!

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*There were also some *related* studies in 1979 by Harold S. Luft and Mark S. Freeland and co-workers.

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Upside-Down Lateral View

To the Editor: With regard to Silverberg, Johnston and Haber's interesting paper on "Tuberculous Involvement of a Polymicrobial Liver Abscess,"[1] I wish to be one of (no doubt) many to draw your attention to the interesting figure accompanying this article. Figure 1 consists of two x-ray views: A, labeled posterior anterior view; B, labeled lateral view. On examination of these figures one must note that Figure A is a completely new technique, not heretofore published to my knowledge—the upside-down lateral view. How is it that we have been deprived in the text of this article of discussion of this remarkable new technique for disclosing liver abscesses?

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Editor's Note

We can only hang our heads in shame.

MSMW

Topics in Primary Care Medicine

The Swollen Leg

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"Topics in Primary Care Medicine" presents articles on common diagnostic or therapeutic problems encountered in primary care practice. Physicians interested in contributing to the series are encouraged to contact the series' editors.

BERNARD LO, MD
STEPHEN J. McPHEE, MD
Series' Editors

Pain and swelling in the lower extremity are common problems seen by physicians in their offices and in emergency rooms. In the 1976 National Ambulatory Medical Care Survey, symptoms referable to the lower extremity represented the fourth most common problem seen by internists and the second most common seen by family and general practitioners. The differential diagnosis for the swollen leg is extensive (Table 1), and the clinical examination is distinctly limited in differentiating one cause from another. Ancillary studies are frequently necessary to make a more specific diagnosis, but inherent in the investigation are costs and potential risk to patients. In this paper we will focus on the major causes of the swollen leg, the utility of and indications for various diagnostic procedures and a strategy for management.

Deep Venous Thrombosis

Of the causes of the swollen leg, deep venous thrombosis is the greatest possible threat to the health of a patient and raises the most important therapeutic considerations. Many studies have documented the limited predictive value of the physical examination in accurately diagnosing or excluding suspected venous thrombosis. Because the presence of pain, swelling and tenderness and a positive Homan's sign are nonspecific, they will not differentiate between the conditions of those patients found to have deep venous thrombosis by contrast venography and those who have normal venograms. Therefore, patients clinically suspected of having deep venous thrombosis must undergo further investigation. The disadvantages of doing more specific tests in all patients in whom venous thrombosis is suggested are the expense of the investigation, the inconvenience to patients and the possible morbidity caused by the tests. However, the cost is substantially less than the cost of unnecessary hospital admission, or prolonged hospital stay, and of unnecessary anticoagulant therapy in patients who have an incorrect diagnosis based on the findings of physical examination alone.

Currently contrast venography is the "gold standard" for the diagnosis of deep vein thrombosis. The diagnosis is made if there is an intraluminal filling defect or nonfilling of a venous segment that is constant in all films. This study can be done rapidly, giving immediate results that are conclusive if the study is technically adequate. Disadvantages of contrast venography include contrast reactions (1% to 3%), local inflammatory responses (25%), inadequate visualization of the iliac veins (2% to 9%), radiation exposure and induction of deep venous thrombosis in patients whose venograms are initially normal (0.3% to 4%). Because of these drawbacks, other diagnostic tests have been evaluated as aids to decision making.

Impedance plethysmography (IPG) relies on the principle that blood volume changes in the calf produced by temporary venous obstruction result in changes in electrical resistance (impedance) that can be detected by skin electrodes placed around the thigh. IPG has been shown to have a sensitivity of 90% to 95% and a specificity of 90% to 98% for proximal (thigh vein) thrombosis but it detects only 20% of distal (calf vein) thrombi, giving it an overall sensitivity of 68% and a specificity of 98%. With a prevalence of deep venous thrombosis of 40%, an abnormal IPG has a predictive value of 96%, and a normal IPG has a predictive value of 82%.

An abnormal IPG is highly predictive of deep venous thrombosis. In patients who do not have conditions known to produce false-positive results and who have no risk factors for complications of anticoagulation, treatment can be initiated without further testing. Causes of false-positive results from an IPG test include poor positioning, poorly relaxed muscles, extravascular compression (such as by tumors or retroperitoneal fibrosis), hypotension, arterial insufficiency and conges-

(Cooney TG, Reuler JB: The swollen leg [Topics in Primary Care Medicine]. West J Med 1985 Mar; 142:405-408)

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TABLE 1.—*Differential Diagnosis of the Swollen Leg*

Deep venous thrombosis
Superficial thrombophlebitis
Popliteal (Baker's) cyst-pseudothrombophlebitis syndrome
Postphlebitic syndrome
Venous insufficiency
Congestive heart failure
Cellulitis
Leg swelling in paralyzed leg
Lymphatic obstruction, lymphangitis
Muscle strain
Muscle tear
Internal derangement of the knee
Fracture
Hematoma
Rhabdomyolysis, myositis
Acute arthritis
Compartment syndromes

tive heart failure. Risk factors for major bleeding during anticoagulant therapy include a history of alcohol abuse and serious concurrent disease. A normal (negative) IPG, because of the high false-negative rate with this test, would necessitate further study.

Fibrinogen leg scanning using iodine I 125 is a very sensitive technique for detecting acute calf vein thrombosis but is insensitive for proximal vein thrombosis. Because of these operating characteristics, leg scanning complements IPG. The combined approach of IPG and leg scanning has been advocated as an alternative to venography. In combination, IPG and leg scanning have a sensitivity of 90% and a specificity of 86%. With a prevalence of deep venous thrombosis of 40%, the predictive value of a positive result for either test is 80%. The predictive value when both tests are normal is 93%. The improved sensitivity of the combined procedures comes at the cost of decreased specificity, primarily due to false-positive results of distal leg scans. False-positive results for leg scans may be caused by hematomas, inflammation (such as cellulitis or superficial thrombophlebitis) or uptake in surgical wounds. In addition, a leg scan can take 72 hours to show abnormalities in patients with venographically documented deep venous thrombosis, a characteristic that greatly limits its usefulness. Finally, leg scans are available in very few hospitals.

Doppler ultrasonography, in expert hands, is a relatively sensitive method for detecting proximal vein thrombosis but is insensitive for detecting calf vein thrombosis. It has an overall sensitivity of 56% and a specificity of 91%. This method has many of the limitations of IPG and involves a more subjective interpretation.

Radionuclide venography, which uses technetium Tc 99m macroaggregated albumin, is a promising test to replace contrast venography. Unfortunately, reports of its accuracy have varied substantially, with sensitivities ranging from 51% to 99% and specificities from 67% to 100%. Advantages of radionuclide venography include very good visualization of the deep venous system, including the pelvic system, lack of complications and immediately available results. Additionally, in cases of suspected pulmonary embolism, this technique may be combined with pulmonary scintigraphy without the administration of an additional injection. False-positive results can occur if a patient has chronic venous insufficiency and extravascular obstruction. False-negative values primarily result from inadequate visualization of the deep veins of the calf.

The optimal diagnostic approach to suspected deep venous thrombosis is dictated by many factors: the location and condition of a patient, the presence of conditions known to produce false-positive test results, the risk of anticoagulation

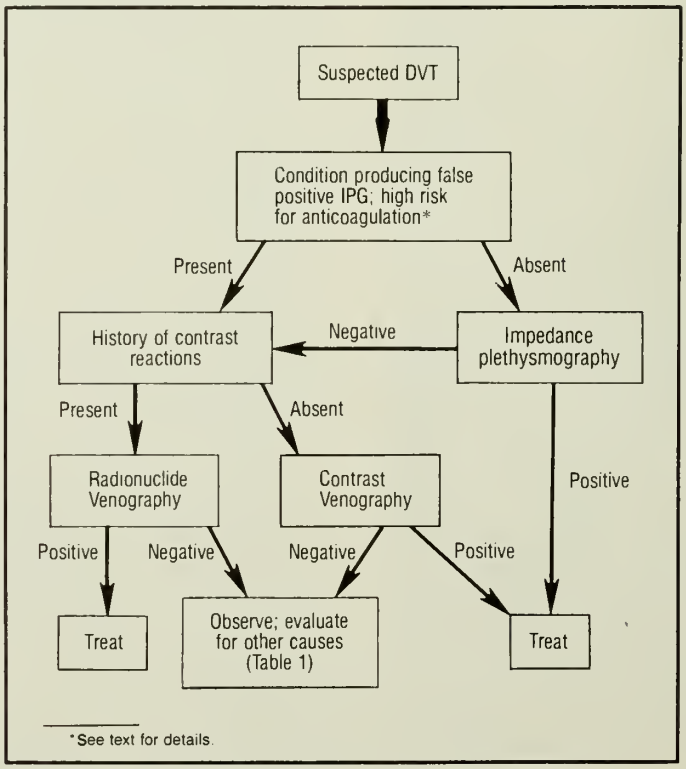

Figure 1.—Diagnostic strategy for deep venous thrombosis (DVT).

in an individual patient and the cost and availability of diagnostic tests, as well as the expertise of those doing the tests.

A diagnostic strategy for ambulatory patients is presented in Figure 1. Implicit in this strategy are several assumptions. One, most cases of distal vein thrombosis should be defined and treated. The clinical significance of distal (calf) vein thrombosis remains undefined. It is thought that most pulmonary emboli arise from the proximal leg veins, pelvic veins and other proximal venous sites. The frequency of pulmonary embolization from isolated calf vein thrombosis is unknown but is estimated to occur in up to 33% of cases. The clinical significance of these pulmonary emboli and the natural history of untreated isolated calf vein thromboses are likewise unknown. At present, 10% to 20% of calf vein thromboses are thought to propagate to more proximal veins, from which the risk of embolization is well established. Moreover, fatal pulmonary embolism from initially isolated calf vein thrombosis has been reported. Until this clinical controversy is resolved, it is probably prudent to identify and treat cases of distal vein thrombosis. However, in certain subgroups of patients who are at higher risk for complications of anticoagulation—such as the elderly and patients with severe intercurrent illness—the risk of anticoagulation may exceed the benefit of treatment. In those patients, clinicians may elect to withhold anticoagulation therapy while carefully monitoring for evidence of proximal propagation of the thrombosis. Two, the risk of a false-negative result with IPG exceeds the risk of doing contrast venography in patients with a normal IPG. Doing serial IPGs in patients who have an initially normal test may be a useful alternative strategy, but this approach requires further validation (see Addendum). Three, an abnormal IPG, when done in those at low risk for anticoagulation and without conditions known to produce false-positive results, has sufficient predictive value to indicate treatment. In this situation, the marginal gain in accuracy achieved by doing confirmatory contrast venography would be exceeded by the risk of complications. Four, the risk of contrast reactions in patients with a previous history of contrast reactions may exceed the risk of false-negative results with radionuclide venography. The addition of leg scanning, or the substitution of IPG and leg scan, if available, would increase the sensitivity of this strategy; however, there would probably be a decrease in specificity and the acquisition of test results would be delayed by 72 hours.

Pseudothrombophlebitis

The pseudothrombophlebitis syndrome is defined as the presence of symptoms and signs of thrombophlebitis in association with a dissected, ruptured or large intact popliteal synovial cyst. Pseudothrombophlebitis has been reported in up to 20% of patients initially thought to have deep venous thrombosis. Popliteal (Baker's) cysts are caused by herniation of synovial membrane through the joint capsule or enlargement of the bursa communicating with the joint capsule. More than 50% originate from either the semimembranous or gastrocnemius bursa. Arthrographically, a dissected popliteal cyst is one extending below the popliteus tendon bursa, whereas a ruptured cyst is one that loses the normally smooth outer margin and releases contrast material into the soft tissues of the calf. The history and physical findings in cases of pseudothrombophlebitis may mimic deep venous thrombosis in every way, and many patients with this syndrome have been treated inappropriately with anticoagulants, leading in some to hemorrhagic complications. Although pseudothrombophlebitis has classically been associated with inflammatory arthropathies, it is now recognized that this syndrome may develop in any form of knee disease, whether clinically evident or not. Subtle trauma—dancing, jogging—and remote injuries to the knee can be key historical features in this syndrome. Although many patients will have a knee effusion, other signs of joint inflammation may be absent. The presence of tenderness, warmth and erythema usually indicate dissection or rupture of the cyst.

Ultrasonography of the popliteal space is quite specific for synovial cysts but lacks enough sensitivity to exclude their presence. Arthrography is the diagnostic study of choice if the results of ultrasound are negative. Occasionally patients may have a normal arthrogram and subsequently be shown to have pseudothrombophlebitis. This may be caused by transient rupture of the lining of the cyst with extravasation of synovial fluid and rapid sealing of the defect.

Because symptoms of a popliteal cyst may mimic deep venous thrombosis, investigation for venous thrombosis is frequently undertaken before a clinician pursues the diagnosis of pseudothrombophlebitis. The coexistence of deep venous thrombosis and pseudothrombophlebitis due to popliteal cysts is well described, so that patients being treated for deep venous thrombosis who do not improve as expected should have a workup for a popliteal cyst. Furthermore, synovial cysts—intact, dissecting or ruptured—can produce venous compression and obstruction of the popliteal and proximal calf veins. While the extrinsic source of this obstruction is evident on contrast venography, it may produce false-positive results with noninvasive studies, particularly with fibrinogen ^{125}I scanning. Management of the pseudothrombophlebitis syndrome includes leg elevation, the use of anti-inflammatory agents and, occasionally, treatment with intraarticular steroids.

In a patient in whom deep venous thrombosis and pseudothrombophlebitis have been excluded, other diagnoses should be considered. Local muscle strains have been diagnosed in nearly 25% of patients initially suspected of having deep venous thrombosis whose contrast venograms have been normal. The sudden development of pain occurring with exertion, particularly unaccustomed exercise, suggests rupture of the plantaris tendon. This may be associated with severe swelling. Less commonly, rupture of the medial head of the gastrocnemius can occur suddenly during exertion. The presence of pronounced calf tenderness during dorsal flexion of the foot with the knee in extension can help differentiate rupture of the medial head of the gastrocnemius from rupture of the plantaris tendon.

The postphlebitic syndrome is a common source of difficulty in the differential diagnosis of a swollen leg. It is characterized by aching in the leg on standing associated with leg swelling, dilatation of venules around the ankle and increased skin pigmentation. It occurs in persons who have had thromboses and damage to venous valves, leading to venous incompetence. It is important to recognize that the postphlebitic syndrome, as well as venous insufficiency, may produce false-positive results in noninvasive tests for deep venous thrombosis.

Cellulitis of the calf may often mimic thrombophlebitis. Erythema, warmth, swelling and tenderness are usually present; lymphangitis and lymphadenitis occur less frequently. A portal of entry is found in less than 50% of cases of lower extremity cellulitis, and a distinct prodrome is seen infrequently. Necrotizing fasciitis is a rare soft tissue infection that produces extensive necrosis of superficial fascia and adjacent tissues. It occurs most commonly in diabetic patients, often associated with only minimal trauma. Gram-negative gas-forming organisms are often isolated. A careful search, clinically and radiographically, for soft tissue gas may aid in early diagnosis of this potentially lethal infection.

Traumatic hematomas and rhabdomyolysis of the calf may present as swelling and pain. These conditions alone, or in association with tibial plateau or long bone fractures, should be particular considerations in a patient with chronic alcoholism who may be predisposed to both trauma and rhabdomyolysis.

An ambulatory patient with swelling in the leg in whom deep venous thrombosis and serious infection have been excluded can be managed at home with leg elevation and anti-inflammatory agents. Despite careful evaluation for the many causes listed in Table 1, nearly 25% of patients with normal venograms will have no specific diagnosis made during follow-up. These patients probably have inflammation of the soft tissues of the leg that cannot be specifically identified.

Addendum

As this article goes to press, a prospective, randomized study of serial impedance plethysmography for clinically suspected deep vein thrombosis has been reported (R. D. Hull, J. Hirsh, C. J. Carter, et al: Diagnostic efficacy of impedance plethysmography for clinically suspected deep-vein thrombosis. Ann Intern Med 1985 Jan; 102:21-28). The findings of this study lend further support to the proposed strategy of doing serial IPGs in selected patients with possible deep venous thrombosis and initially normal IPG.

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Culture Shock—A Review of Vietnamese Culture and Its Concepts of Health and Disease

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Misunderstandings of Vietnamese culture and beliefs have led to many unfortunate incidents in the United States, including court cases for child abuse and even suicide. These can be avoided by an awareness of the cultural background of the Vietnamese, their philosophy of life and the influence of religion and beliefs on their personalities, both as individual persons and as members of extended family units. The Vietnamese concepts of health and disease are presented, along with brief descriptions of certain folk medicines that are frequently misconstrued by American physicians.

(Nguyen D: Culture shock—A review of Vietnamese culture and its concepts of health and disease [Cross-cultural Medicine]. West J Med 1985 Mar; 142:409-412)

From April 1975 through February 1982, about 1.4 million Indochinese refugees fled their homelands. Nearly 580,000 (40%) of these refugees, most of whom were Vietnamese, have settled in the United States.[1] They have incurred, in turn, a host of cultural, economic, political, psychological and social upheavals.[2]

In contrast to the nearly 1 million Cuban refugees that have settled in the United States since January 1959, the Vietnamese refugees have had to confront more immediate problems: They had no previously settled ethnic group to offer initial support; their culture was more dissimilar to that of the Americans, and they have frequently been symbolically identified with the unpopular Vietnam war. In brief, their arrival in the United States marked the beginning of a long and arduous process of adjustment to a new life in a new country with an alien culture.

Inevitably, misunderstandings have occurred. For example, a Vietnamese father took his 3-year-old son to an American hospital because of possible influenza.[3] The child had many ecchymoses on his chest and back, and the father was suspected of child abuse. Although he explained that the ecchymoses represented *cao gio*—that is, a home treatment of coin rubbing—he was jailed and subsequently committed suicide.

In the hope that such misunderstandings can be avoided, I will briefly review the cultural background of the Vietnamese; describe the Vietnamese both as individual persons and as members of extended family units; discuss Vietnamese religious beliefs and social heritage, and present the traditional Vietnamese health beliefs.

The Oriental Heritage

"East is east and west is west." The Oriental cultures and values differ considerably from those of Americans. For example, American civilization has thrived on overcoming and mastering nature, whereas the Indochinese cultures stress harmony with nature. Instead of towering skyscrapers, the ancient Asians constructed their houses not by height but to blend modestly with the environment, creating thereby a sense of tranquility with life. Even today, Indochinese persons aspire to have the trees, grasses, mountains and rivers provide warmth and protection for their houses, in the hope that nature will be supportive of their lives and their families.[4]

Moreover, the Oriental daily life-style is less stressful. People tend not to rush because their concept of time is much more elastic. In contrast to the almost compulsive punctuality of Americans, Oriental persons frequently arrive late for appointments.

Vietnamese as Individuals

Vietnamese have but a few family names for a population of 56 million persons (1982 figure), with Nguyen being the most common. Their names are always written in the following order: family, middle (sometimes twice) and first names. This order may create confusion for medical records keeping and is frequently a source of misunderstanding. Also, they are typically addressed by their first names (even by strangers), a practice that is occasionally denigrated by Americans.

A person's age is also a source of confusion. For Vietnamese, it is calculated roughly from conception. Thus, most

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children are considered to be a year old at birth and gain thereafter a year at every lunar New Year—that is, each Tet. For example, a child could be 2 years old by Vietnamese counting, but less than a month of age by American reckoning.

Because of the strong influence of the Confucian code of ethics, proper form and appearance are very important to Vietnamese. For example, the head is considered to be the sacred part of the body; therefore, it is most impolite to pat the head of a Vietnamese adult. Similarly, the feet are the lowest part of the body; thus, a Vietnamese person will feel offended if an interlocutor places an imprudent foot on the desk pointing towards him or her. Again, to signal for someone to come by using an upturned finger is a provocation (usually done to a dog); waving the hand is considered to be more proper.

Both Confucian and Buddhist beliefs urge Vietnamese persons to be shy and modest. They rarely display strong emotions in public. Hugging and kissing are not seen outside the privacy of the home, and the sight of a wife being hugged by casual friends in public is a major source of discomfort for a Vietnamese husband.

The Vietnamese Family Unit

Because American culture stresses individualism, Americans find it difficult to fully understand the power of kinship for Vietnamese. The family is the fundamental social unit—that is, the primary source of cohesion and continuity—in traditional Vietnamese society. Differing profoundly from the American nuclear family, the Vietnamese family should be perceived as "a superorganic unit existing across generations past and future."[5] The crux of family loyalty is filial piety, which commands children to honor their parents. One's behavior, for better or for worse, reflects not only on oneself but also on the family itself.

The family may be involved in health care decisions, and they may not leave such a decision solely to the patient. As Tran, a well-known Vietnamese psychiatrist, noted, "In most cases, the relatives, more than the patients, are the ones to be convinced before the patient can start or continue a therapeutic program."[6]

Most Vietnamese refugees arrived with a large patriarchal household of 5 to 12 members, including the core (nuclear) family, the grandparents, some siblings (and their families) and even some in-laws. For those families that stayed together, life has not been without problems: Prolonged closeness often creates friction, cumpulsory intimacy may generate personal irritations, exposure of the younger generation to the American culture frequently becomes a source of conflict and incessant expectations of mutual dependency may become hateful obligations and a common origin of emotional illnesses.

When such conflicts arise, the unhappiness will initially be suffered in silence and in privacy. Such behavior is fostered by an enduring Buddhist and Confucian pattern of conduct that encourages passiveness and personal reserve. But a gradual eroding of these cultural influences, coupled with increasing conflicts within families, may cause the unhappiness to evolve rapidly into overt crises. The eventual outcomes are more likely to be radical and disruptive—such as separation or divorce—instead of being mediated by compromise, resignation or tolerance (as in the past in Vietnam).

Religious Beliefs

The Vietnamese are strongly influenced by several sets of religious beliefs.[7] First, Buddhism was introduced to Vietnam as early as the second century AD. Its influence is essentially the creation of a state of mind (rather than compulsory attendance at an established church). Central to this faith is a concept of life in which suffering is caused by desire. Desire can be eliminated by correct behavior—that is, the "Eight-Fold Path"—which lessens one's suffering in life. For example, some Vietnamese may quote Buddha's teachings about the world as a cycle of ordeals: to be born, grow old, fall ill and die.

Second, Confucianism is more a way of life than a religion per se. Involving a code of ethics and morals, it emphasizes the hierarchy of the members of society and stresses the worship of ancestors.

Third, originating from Lao-tzu (a 6th century BC philosopher), Taoism has also had an important role in the development of the Vietnamese cultural personality. Taoism is "naturalism" in the sense that it advocates taking no unnatural action to achieve conformity to the *Tao* ("the Way"). This philosophy stresses that, when things are permitted to assume their natural course, they move toward perfection and harmony.

Fourth, Catholicism and Protestantism were more recently introduced to Vietnam, but they are followed by only a minority of the Vietnamese.

Finally, animistic belief is much less frequently invoked by the Vietnamese than in the past. However, it is still practiced by the mountain tribes—that is, the "montagnards"—in the highlands of Vietnam.

The Vietnamese Cultural Personality

Such religious concepts and beliefs as mentioned above have been transmitted through the generations to produce an attitude towards life that may be perceived as passive. For example, whenever confronted with a direct but delicate question, many Vietnamese cannot easily give a blunt "No" as an answer, because they feel that such an answer would create disharmony. In such a context, "Yes" tends to reflect either an avoidance of confrontation or a desire to please the addressee, rather than an affirmation of truth.

Self-control is another traditional value of the Vietnamese. Emotions are typically kept to oneself, whereas expressions of disagreement that may irritate or offend are avoided. They may be in pain, distraught and unhappy, yet they rarely complain (except perhaps to friends or relatives). There are also deep cultural restraints against showing "weakness" of the mind. Emotions are considered weaknesses because they interfere with self-control. Superior persons, therefore, should not be swayed by emotions nor, even less, permit other persons to see that they are troubled by intimate feelings. Hostility is not usually expressed towards persons who are considered superior—such as parents, physicians or teachers. American health services personnel may comment that their Vietnamese patients rarely appear desperate or depressed, but seem reasonably content, frequently

smiling and seldom complaining or demanding—that is, they have "the good patient look."[8]

The next step in self-control for nearly all Vietnamese persons is denial and avoidance. If pain and sorrow inevitably occur, one should try to forget them and hope for the best. What often sustains this effort against being overwhelmed by desperation is a special form of rationalization: "destiny." It was "destiny" when they were saved, when they were able to escape to liberty rather than being detained in a concentration camp. It is also destiny when misery is prolonged for some but shorter for others. Accepting one's destiny means resignation, but it also suggests hope: Things may improve anytime, if it is one's destiny for events to change at that particular moment.

The final step is fatalism. When one's life cannot be saved, this is accepted stoically. In the older Vietnamese generations, it was hardly uncommon to see a house with a coffin situated beneath the household altar. Knowing that the days were short, the owner bought his or her future coffin. That is, a person must think about impending death, foreseeably prepare for the final moment and accept the final coming of death. The burial site may even have been chosen, because the position of the land can have an effect on the children. So, during the final days of life, a person will polish the coffin and even decorate it for the future eternal trip.

In summary, unlike Americans who look to the future and plan for progress, Vietnamese cherish and uphold their ties with the past and their historical heritage of "4,000 years of civilization." While Americans are goal-oriented, Vietnamese prefer activities that develop the human essence, such as philosophy, poetry and meditation.

Vietnamese Traditional Health Beliefs

Vietnamese will frequently use folk treatments either concurrently or before seeking Western medical care.[9] Those folk treatments are particularly influenced by the Chinese concepts of yin and yang. That is, the universe—and thus a human being—is composed of two dynamically opposing forces: the masculine (yang), as represented by light, strength and heat; the feminine (yin), as represented by darkness, softness and cold. An excess in either direction will lead to disequilibrium and the production of disease.[10] Certain diseases are said to result from an excess of the cold element, such as diarrhea which is attributable to a "cold" stomach. Other diseases are ascribed to an excess of the hot element, such as pimples or pustules which are attributable to an excess of a hot element erupting through the skin. Similarly, foods are divided into two groups: hot—spices, coffee, beef, wild game—and cold—tea, most fruits, chicken, duck, seafood.

Drugs and medicinal herbs are also carefully classified according to their properties along a scale of hot and cold effects. From this concept, a number of techniques for the cure of illnesses have evolved:

- *Cao gio,* "coin rubbing" with hot balm oil that produces ecchymotic marks and petechiae on the chest and back.[11] (This has, unfortunately, been a source of many accusations of child abuse leading to court trials and even suicide.) The Centers for Disease Control have recently been asked to evaluate the effectiveness of this practice.[12]
- *Be bao* ("skin pinching"), a derivative of the above practice.
- *Giac* ("cup suctioning"), with or without prior scarification.
- *Xong* (herbal steam fumigation).
- Balm application (Tiger's balm, *Mac Phsu Cula* or *Nhi Thien Duong* oil).
- Ingestion of herbal concoctions, an influence of traditional Chinese medicine.
- Ingestion of organ meats. For instance, consumption of animal liver produces a strong liver, and so forth for brains, kidneys and testis. Many Vietnamese also believe that eating the gelatinous product of tiger bones (produced by prolonged cooking) will make them strong.
- Ingestion of hot food to cure cold illness and vice versa (chicken soup is recommended for the treatment of fever).
- Finally, other health practices have obscure origins. For example, a diet heavy in salt is believed to be good for pregnant women, and postpartum women should sleep over a charcoal heater to shorten the postdelivery period.

Besides these examples of folk medicine, Vietnamese readily use Western medicine (often both concurrently). Self-medication is a popular medical behavior in Vietnam. One does not need prescriptions to purchase medicines at drugstores in Vietnam, which may partially explain the increasing resistance of bacteria to several readily available antibiotics. Vietnamese also prefer drastic treatments: They believe strongly that a shot (intramuscular injection) is superior to a common oral preparation, and many ask for the 5% dextrose in water solution (called "sea water") to be given intravenously for rapid recuperation from illness.

Because medicine usually deals with invisible and immaterial elements, Vietnamese rarely feel a need for invasive techniques or surgical procedures. Surgical operations are perceived as a last resort; they are usually equated with admission to hospital, which is, in turn, associated with death (and thus to be avoided).

Because of the previously mentioned religious beliefs and because of deep cultural restraints against showing a "weakness of mind," an extremely small percentage of the Vietnamese population avail themselves of mental health services. Psychiatry and mental health are terra incognita for the vast majority. A psychiatrist is either a "nerve doctor"—which underscores the biologic label attached to the specialty—or a "doctor for the insane"—which emphasizes the bizarre, "out-of-this-world" character of mental diseases. In brief, then, delays in seeking medical care (both mental and physical) due to stoicism are a negative aspect of the Vietnamese cultural heritage.

Conclusion

Misunderstandings will inevitably occur whenever two cultures coexist. I have reviewed the differing aspects of the Vietnamese cultural heritage in the hope that further unfortunate incidences such as the child abuse accusations and subsequent suicides can be avoided. The Vietnamese in the United States are refugees—and, by definition, are involuntary immigrants. Their expatriation was unexpected, their trip was unplanned and their departure from Vietnam was precipitous. Hence, the absence of any material or psychological preparation meant that the impact of transplantation could not be cushioned.

Of course, the Vietnamese will adjust, but the cost of

adjustment will necessarily vary with the situations involved. The most sensitive situations require awareness of the basic values, beliefs and traditions that have been imprinted for an entire lifetime. For American health professionals, a knowledge about Vietnamese cultural heritage, even if sketchy, should further their capacities for empathy, tolerance and compassion so that they will see Vietnamese patients as persons culturally worthy of attention and respect.

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Commentary

Sherlock Holmes's Methods of Deductive Reasoning Applied to Medical Diagnostics

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Having patterned the character of Sherlock Holmes after one of his professors, Sir Arthur Conan Doyle, himself a physician, incorporated many of the didactic qualities of the 19th century medical diagnostician into the character of Holmes. In this paper I explore Holmes's techniques of deductive reasoning and their basis in 19th and 20th century medical diagnostics.

(Miller L: Sherlock Holmes's methods of deductive reasoning applied to medical diagnostics [Commentary]. West J Med 1985 Mar;142:413-414)

When I started reading the Sherlock Holmes stories, I was immediately struck by the similarities between what Holmes called deductive reasoning and what I was trying to do while making medical diagnoses. This casual observation was no mere coincidence. Sir Arthur Conan Doyle, himself a physician, patterned the fictional character of Holmes after one of his professors, Dr Joseph Bell, an expert in medical diagnostics. Doyle used basic theories of medical diagnostics to create his character's uncanny ability to reason in a deductive manner.

Sherlock Holmes epitomizes the logical thinker and teaches us more about deductive reasoning than any other character, literary or real. As physicians, if we read between the lines of Doyle's famous stories, we can learn a good deal about the art of medical diagnostics.

Fitzgerald and Tierney's article, "The Bedside Sherlock Holmes,"[1] was fascinating, but they did not fully explore the similarities between the methods of a criminal sleuth and a medical sleuth.

Medical diagnostics, deductive reasoning or good sleuthing can be divided into four basic processes: gathering facts, sorting facts, formulating differential diagnoses and arriving at solutions.

Gathering the Facts

The world is full of obvious things which nobody by any chance ever observes.

THE HOUND OF THE BASKERVILLES, II:669-761*

Observation is the key to gathering the facts, and the facts are what we build logical inference and theory upon.

To gather the facts, we must first know what we are looking for. This depends on the type of investigation we undertake, but, no matter what kind of investigation, there are only two ways to obtain data. The first is by verbally interviewing people (taking the history). The second is by carefully scrutinizing objects (the physical examination). The practice of medicine usually depends heavily on the history.[2]

The facts must be gathered in great depth and breadth. Every detail must be scrutinized and described as accurately as possible. Facts must be described in this manner, first, because they may be transient. An observed fact will remain documented even if events change; an unobserved fact may be substantially altered when the observer next encounters it. Examples of transient facts include footprints in the mud, a transient seizure or a person's memory of seemingly inconsequential events.

Gathered facts can be sorted later and the wheat separated from the chaff. Ungathered facts will not profit the observer and will eventually be lost. To quote Holmes, "They say that genius is an infinite capacity for taking pains. It is a very bad definition, but it does apply to detective work" (*A Study in Scarlet*, I:15-46).

Second, just as the presence of certain facts may lead to certain conclusions, the absence of certain facts may be significant and lead to other conclusions. If facts are absent, let them be absent because they did not exist, not because we neglected to collect them.

As the facts are gathered, they will ultimately lead the investigation in certain directions. This, of course, is necessary, but there is a pitfall. Value judgments must be withheld until all the facts have been gathered and sorted, for faulty conclusions are drawn from insufficient data. In one of Holmes's more modest moments he admits, "I had come to an entirely erroneous conclusion, which shows, my dear Watson, how dangerous it always is to reason from insufficient data" (*The Speckled Band*, I:257-273). One would not call painless jaundice cholelithiasis without excluding by ap-

*All of the Sherlock Holmes references in this article are from A.C. Doyle, *The Complete Sherlock Holmes*, Volumes I and II, published by Doubleday and Company, Inc, 1930. Only the volume and chapter page numbers will be given.

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propriate diagnostic techniques the possibility of biliary obstruction due to pancreatic cancer. I can state this no more eloquently than did Holmes: "It is a capital mistake to theorize before you have all the evidence" *(A Study in Scarlet).*

Sorting the Facts

> *I can never bring you to realize the importance of sleeves, the suggestiveness of thumb-nails, or the great issues that may hang from a bootlace.*
>
> A CASE OF IDENTITY, I

The next process in deductive analysis is to sort the facts—to eliminate facts unnecessary to the investigation and to list positive findings and pertinent negative findings.

How does one go about sorting trivial from meaningful facts? The answer is experience in the field in which one is working. Sherlock Holmes was an expert in his field. "As a rule, when I have heard some slight indications of the course of events I am able to guide myself by the thousands of other similar cases which occur to my memory" (*Red-Headed League,* I:176-190).

As explained by DeGowin and DeGowin,

> As new facts are acquired by any means, the physician repeatedly tests them for reliability. He must conclude whether the items are trivial or relevant to the identification of the patient's disease. From the accumulated facts he must select for further consideration those symptoms and signs that his experience has taught are most likely to be helpful clues.[3]

Differential Diagnosis

> *It is a capital mistake to theorize before one has data. Insensibly one begins to twist facts to suit theories, instead of theories to suit facts.*
>
> A SCANDAL IN BOHEMIA, I:161-176

Now that one has all the positive findings listed, one may go on to formulate explanations to fit the facts.

From where do these explanations come? The explanations that are formulated come from a store of information that the investigator has accumulated (a file of information). The file may be a physical file, a library of information or a reservoir of memories.

We can train ourselves to observe and through experience we can learn to sort facts, but accumulating a file (the knowledge or store of information) on which to base one's theories is a lifetime pursuit.

Sherlock Holmes, speaking of the French detective Francois le Villaid, says,

> He has considerable gifts himself. He possesses two out of the three qualities necessary for the ideal detective. He has the power of observation and that of deduction. He is only wanting in knowledge; and that may come in time (*The Sign of the Four,* I:89-143).

Arriving at a Diagnosis

> *It is an old maxim of mine that when you have excluded the impossible, whatever remains, however improbable, must be the truth.*
>
> THE BERYL CORONET, I:301-316

The hard work is done and the pieces of the puzzle should now fall into place. We have a list of positive findings and a list of possible explanations. All we need do is fit the explanation to the findings. If we have a fact that contradicts one of our presumptive explanations, then our explanation is faulty and must be eliminated. When we are left with one explanation that fits all of our facts, then we have reached our final solution.

We must always take care to dismiss explanations that contradict facts and not discard facts that contradict explanations. As Holmes explains, "I can discover facts, Watson, but I cannot change them" (*Thor Bridge,* II:1054-1070). We must also beware not to violate the law of parsimony by accounting for a set of facts with numerous explanations. To explain a whole set of facts with one explanation is the trick.

Conclusion

If approached in a random manner, medical diagnosis is a chore; if approached in a systematic, logical manner, medical diagnosis is an intellectual exercise, much like detective work.

Once we know how to look at and solve problems in an organized manner, we are forever drawn into the art of deductive reasoning. To quote Holmes one last time, "The faculty of deduction is certainly contagious, Watson" *(Thor Bridge).*

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Public Health and Preventive Medicine

Measles Transmission in Medical Facilities

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One of a series of articles from western state public health departments.

In 1983 a measles (rubeola) outbreak in a central California county totaled at least 70 confirmed cases, continuing through ten generations of transmission before terminating. The initial two cases recognized in the outbreak infected a total of seven persons in various hospital emergency rooms and medical offices while seeking treatment. Had these transmissions been prevented, the outbreak might have been aborted and thus its most tragic consequence, a teenaged boy whose illness was complicated by encepalopathy with major long-term sequelae, might have been averted.

In all, 31 (44%) of the patients were preschoolers, 14 (20%) were of school age and 25 (36%) were aged 19 years or older. The vast majority of the non-school-age patients had not previously been immunized against measles. At least 20 of the patients probably or certainly acquired their infection in medical facilities. Typically, a person would arrive at an emergency room or medical office shortly before or after rash onset, at a time when measles is extremely infectious by the airborne route, and expose many other patients and medical staff while sitting in waiting rooms, in treatment rooms or in lines for x-ray or other laboratory tests. Five of the nosocomially acquired cases were in young adult medical and paramedical staff members. All of these staff members were quite ill. One of them infected four other persons while seeking treatment himself, and, when spread cases from those four contacts are considered, accounted for a total of 11 cases.

Two other states—Florida and Oklahoma—have reported that nosocomial transmission played a major role in recent measles outbreaks (state public health directors, unpublished communications). In a 1982 Michigan outbreak, airborne spread of infection was found to have continued for more than an hour after a measles patient had left a physician's office.[1] Though measles has become a relatively rare disease in the United States, outbreaks continue to occur, and transmission of the virus in medical settings appears to be a significant factor in multiple outbreaks. Nosocomial transmission is of particular concern because patients who acquire infection in this fashion tend to be very young children or adults, the age groups wherein the measles complication and case-fatality rates are highest.

The risk of nosocomial measles transmission can be reduced considerably by action in three areas:

• *Routine measles immunization of new medical facility staff members born since 1956 (the vast majority born earlier are immune to measles) who lack documentation of prior immunization or disease.* Serologic surveys in California have indicated that, currently, perhaps 10% to 15% of young adults (ages 18 to 22 years) are susceptible to measles.[2,3] Persons in this age cohort often escaped natural measles infection, which has become much less common over the past two decades, and either were not immunized or were inappropriately or inadequately immunized—that is, with killed measles vaccine (which is no longer used), with further attenuated live vaccine administered concurrently with immune globulin, with live measles vaccine that was not handled or stored properly or at younger than 12 months of age (persisting transplacentally derived maternal antibody can interfere with measles immunization in infants younger than age 12 months).[4] The currently used live measles vaccine is a very safe product in both adults and children. Furthermore, reimmunization of persons who are already immune by virtue of prior infection or immunization with the live vaccine poses no enhanced risk, and reimmunization of persons who have previously received only the killed measles vaccine (who are few in number) usually presents only a risk of mild local injection-site reactions.[5] Hospitals, clinics and physicians' offices should, if they do not require it, at least strongly encourage medical facility staff members born since 1956 who have contact with patients—physicians, nurses, aides, laboratory technicians, receptionists, students and the like—and who lack written documentation of prior measles immunization (such as a record showing at least the month and year the vaccine was received) or of prior physician-diagnosed measles disease, to receive measles vaccine. Many hospitals require rubella immunity of personnel, and use of the combined measles-rubella or measles-mumps-rubella vaccines in staff who need rubella immunization can further reduce the risk of measles infection.

• *The Hospital Infection Control Program at the Centers for Disease Control has pointed out that nosocomial transmis-*

(Dales LG, Kizer KW: Measles transmission in medical facilities [Public Health and Preventive Medicine]. West J Med 1985 Mar; 142:415-416)

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sion possibilities should be reduced if outpatients with suspected communicable diseases, particularly those suspected of having infectious illnesses, such as measles, that can be spread by the airborne route are identified at the admission-registration desk and are promptly placed in separate rooms so that they do not sit in open waiting rooms for treatment, x-ray or other laboratory tests.[6] The physical layouts and patient loads of some medical facilities are such that routine, complete isolation of all outpatients with acute rash or febrile respiratory illnesses may be difficult. However, even in these facilities temporary use of such isolation procedures during recognized respiratory disease outbreaks is often possible. In the measles outbreak described at the beginning of this article, institution of isolation procedures in the medical facility where most of the cases were seen was followed by a sharp drop in nosocomial transmission.

• *Prompt telephone reporting of possible measles cases to health departments and cooperation with health departments in containment efforts.* Cases meeting the clinical criteria for possible measles—a temperature of 38°C (101°F) or higher; generalized rash; one or more of the following: cough, coryza or conjunctivitis, and no other established cause—should be handled as follows:

1. Keep the patient isolated in a separate room. If the patient has to be moved from the room, having him/her wear a disposable surgical mask may decrease spread of the virus.

2. Obtain during the acute phase and refrigerate a serum specimen for measles serology. The health department can often arrange for collection of a specimen during the convalescent phase.

3. Identify other clinics or locations in the medical facility that the patient may have visited.

4. Identify other patients born since 1956 who were in the same room (including waiting rooms) as the patient, as well as possibly susceptible staff who were exposed.

5. Call the health department as soon as possible; give the information obtained on the suspected measles case and on other persons possibly exposed to the disease.

6. The health department can work with the medical facility on identification and follow-up of exposed persons: ascertainment of susceptibility status, immunization, isolation and surveillance. Measles vaccine given within three days after exposure or immune globulin (0.25 ml per kg, or 0.11 ml per lb, intramuscularly, to a maximum of 15 ml) given within six days after exposure, can prevent illness or reduce severity of symptoms.

Inpatients with known or suspected measles disease should be kept in respiratory isolation (private room with door closed, staff use of masks, respiratory secretion precautions) for four days after rash onset. Only immune staff should attend these patients. Possibly susceptible inpatients exposed to measles cases should be cohorted for at least 15 days after exposure unless they can be discharged earlier.

Prompt action can avert or curtail measles outbreaks, thereby avoiding the tragic consequences that can accompany this preventable disease.

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Information

Patient Understanding of Oral Contraceptive Side Effects

NORBERT GOLDFIELD, MD
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A PATIENT'S PERCEPTION of the side effects of a medication or complications that might ensue as a result of taking a medication is an important factor in drug compliance.[1] Past research has indicated that half of those given long-term medication comply with the regimen.[1] We examined sources of information, patient perception and compliance with an oral contraceptive regimen prescribed solely for birth control purposes. In particular, we were interested in the role the partner plays in providing contraceptive information and in patient understanding of the side effects of oral contraceptive use. We hypothesized that most patients would place a greater emphasis on side effects that might alter their body image over physically serious contraceptive complications such as blood clots.

Patients and Methods

A self-completion questionnaire was administered to 145 consecutive adolescent and young women attending a group of private nonprofit health centers (Community Health Projects, Inc). The patients received and completed the questionnaires two hours after coming to the clinic for their visit. Patients would receive birth control information[2] on entering the clinic, but were not told that they would be asked to fill out a questionnaire at the completion of their visit.

All effects of taking contraceptive pills, whether complications such as blood clots, side effects such as weight gain or possible associations such as carcinoma were listed under the same heading, "side effects." Patients were asked whether they considered these and other outcomes as "side effects of oral contraceptives." Patients also were asked to complete the statement: "The side effect of birth control pills I am most concerned about is . . ." All complications were listed under one heading, both to test patient judgment as to which side effect was of greatest concern and to simplify the questionnaire for patient understanding. In the questionnaire, race was coded as black, white, hispanic or oriental. Questions were either multiple choice, fill-in-the-blank or true-false. The results of these questionnaires are shown in Tables 1, 2 and 3.

(Goldfield N, Neinstein L: Patient understanding of oral contraceptive side effects [Information]. West J Med 1985 Mar; 142:417-418)

From the Departments of Internal Medicine (Dr Goldfield) and Pediatrics (Dr Neinstein), University of Southern California School of Medicine, and the Division of Adolescent Medicine, Children's Hospital of Los Angeles (Dr Neinstein). Dr Goldfield is now Medical Director, Cigna Corp, Hartford, Connecticut.

Reprint requests to Norbert Goldfield, MD, Medical Director, Cigna Corp, A-110, Hartford, CT 06152.

Discussion

Though these birth control pill users believed that weight gain is a birth control pill side effect (98.6%), they were much more concerned about the physically serious complications of oral contraceptive use such as blood clots. Even though the patients perceived weight gain as a side effect, relatively few believed that this affected them personally.

The belief that birth control pills caused cancer was the primary concern of almost one third of patients. Furthermore, 68.3% of those responding felt that taking birth control pills can cause cancer. In our clinical experience this undocumented feared side effect is often a critical block in encouraging pill usage, especially among teenagers. Blake has reported that negative media reporting increases the noncompliance rate.[3] Minor side effects such as weight gain, headaches, nausea and acne concerned the respondents the least.

In summary, the respondents were more concerned about major side effects, either documented (blood clots) or undocumented (cancer), than possible alterations to their body, weight changes or acne. This negated our hypothesis that patients would be more concerned about typical adolescent concerns (such as weight gain) than more serious physical complications.

The bulk of the information about the side effects of birth control pill use comes from medical offices (51%). Primary care physicians can do more, however, as evidenced by patient fear of the connections between birth control pills and cancer. The family plays a limited role in birth control pill education. This lack of influence may lead to conflict between patient and family if and when the federal government implements its new guidelines on parental consent for prescription of birth control pills to minors. Partners provided the

TABLE 1.—*Side Effects of Birth Control Pills as Perceived by 145 Women Patients of a Group of Private Nonprofit Health Centers*

	Percent
Median age of clinic patients: 20.3 years	
Ethnicity of clinic patients	
White	77.0
Black	12.0
Hispanic	9.0
Asian	1.0
Birth control pill side effects of greatest concern	
Blood clots	46.4
Carcinoma	30.5
Weight gain	15.7
Heart trouble	7.4
Birth control pill side effects of least concern	
Weight gain	67.9
Headaches	15.0
Nausea	9.4
Acne	7.6
Weight change since taking birth control pills	
Increased	57.4
Decreased	42.5
Relation of birth control pills to body image	
Body image improved	16.6
Body image stayed the same	63.9
Body image became worse	19.4

TABLE 2.—*Results of Questionnaire Administered to Health Center Patients**

Statement: "Birth control pills cause __"	*True Percent*	*False Percent*
Carcinoma	68.3	31.7
Blood clots	95.8	4.2
Headaches	79.5	20.5
Acne	37.7	62.3
Weight changes	98.6	1.4
Brain tumors	26.0	74.0
Birth defects	62.5	37.5
Change in menstrual periods	98.5	1.5
Stroke	62.2	37.8
High blood pressure	84.6	15.4
Breast carcinoma	59.6	40.4
Depression or mood changes	87.2	12.8

*Patient population is described in the text and is the same as in Table 1.

TABLE 3.—*Source of Patients' Birth Control Information, and Their Compliance With the Birth Control Pill Regimen**

	Percent
Information received from	
Clinic	27.0
Printed matter from other clinics	24.0
A friend	17.5
A family member	9.0
School	8.9
Other family planning sources	6.9
Television	4.6
Boyfriend	1.6
Compliance of this population with the birth control pill regimen	
No pills missed	76.7
One missed	13.3
Two missed	8.0
More than two missed	1.7

*Patient population is described in the text and is the same as in Table 1.

information to less than 2% of these patients. This finding tends to support the widely held belief that contraception remains the responsibility of the female partner.

This population sample had a high degree of drug compliance. Studies of compliance with other medications that relied on the completion of a questionnaire by patients did not have such a high degree of compliance.[4] Studies of patient compliance with a contraceptive regimen show a range of 14% to 56% noncompliance.[5,6] This indicates the need for continued monitoring of compliance on the part of private physicians. A study of women about to undergo an abortion showed that several had discontinued oral contraceptive use either because of perceived side effects or because physicians advised them to discontinue birth control pill use after they had taken them for several years.[7] Strategies to increase compliance include education (clinic information, slide tape shows), informational medication packaging (although most packets already have very clear package inserts), increased patient supervision, behavior modification (most teenagers view the avoidance of pregnancy in abstract terms) and improving the physician-patient relationship.[8]

Past research has shown that contraceptive compliance positively correlates with desired family size,[9] higher educational attainment,[10] continuous tablet therapy (versus a 21-day regimen),[11] fewer side effects[12] and client instruction.[13] Unfortunately many of these studies were done in developing countries and may have limited relevance for the American population. Further studies will be needed to elucidate whether the relatively high compliance seen in this study was caused by a heightened concern about pregnancy, the ease of using a once-a-day regimen or other factors.

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In Memoriam

California Medical Association

CAMPBELL, CHARLES A., Palo Alto. Died October 7, 1984, at Stanford University Hospital of cancer, aged 77. Graduate of the University of Cincinnati College of Medicine, 1937. Licensed in California in 1954. Dr Campbell was a retired member of the Santa Clara County Medical Society.

COBURN, RAUDEN HOWELL, Fresno. Died November 11, 1984, aged 74. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1938. Licensed in California in 1938. MD degree from California College of Medicine, 1962. Dr Coburn was a retired member of the Fresno-Madera Medical Society.

COOPER, BASIL J. W., Alamo. Died October 24, 1984, in Walnut Creek, aged 52. Graduate of McGill University Faculty of Medicine, Montreal, 1958. Licensed in California in 1966. Dr Cooper was a member of the Alameda-Contra Costa Medical Association.

FLANDERS, JACKSON, Redwood City. Died October 21, 1984, in Los Gatos, aged 82. Graduate of Harvard Medical School, Boston, 1929. Licensed in California in 1946. Dr Flanders was a retired member of the San Mateo County Medical Society.

FOGLE, HAROLD W., San Pedro. Died October 2, 1984, aged 54. Graduate of the University of Michigan Medical School, Ann Arbor, 1956. Licensed in California in 1957. Dr Fogle was a member of the Los Angeles County Medical Association.

IKENBERRY, MAURICE L., Long Beach. Died September 25, 1984, in Baja, Mexico, aged 60. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1951. Licensed in California in 1951. MD degree from California College of Medicine, 1962. Dr Ikenberry was a member of the Los Angeles County Medical Association.

KWINT, JOSEPH A., La Jolla. Died September 8, 1984, aged 72. Graduate of the University of Illinois College of Medicine, Chicago, 1937. Licensed in California in 1949. Dr Kwint was a retired member of the San Diego County Medical Society.

LEE, JOHN C., Sacramento. Died October 17, 1984, of cancer, aged 58. Graduate of the University of Cincinnati College of Medicine, 1951. Licensed in California in 1952. Dr Lee was a member of the Sacramento-El Dorado Medical Society.

MORGANS, PHILIP M., Chico. Died October 5, 1984, of leukemia, aged 72. Graduate of the University of California Medical School, Berkeley-San Francisco, 1946. Licensed in California in 1946. Dr Morgans was a retired member of the Butte-Glenn Medical Society.

THORNTON, WILLIAM HARRY, San Andreas. Died October 29, 1984, in San Andreas, aged 70. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1944. Licensed in California in 1944. MD degree from California College of Medicine, 1962. Dr Thornton was a member of the San Joaquin County Medical Society.

Idaho Medical Association

ALKIRE, LEONARD, Boise. Died February 10, 1984, in Espanola, New Mexico, aged 55. Graduate of the University of Nebraska College of Medicine, Omaha, 1953. Licensed in Idaho in 1966. Dr Alkire was a member of the Ada County Medical Society.

CORNELL, DALE DUANE, Boise. Died May 3, 1984, aged 74. Graduate of the University of Iowa College of Medicine, Iowa City, 1935. Licensed in Idaho in 1947. Dr Cornell was a member of the Ada County Medical Society.

ELLIS, PAUL MARVIN, Wallace. Died January 1, 1984, in Wallace, aged 86. Graduate of the University of Oregon Medical School, Portland, 1929. Licensed in Idaho in 1930. Dr Ellis was a past president of the Idaho Medical Association and a past president and member of the Shoshone County Medical Society.

HOLSINGER, HAROLD F., Wendell. Died October 27, 1984, in Wendell, aged 77. Graduate of the University of Oregon Medical School, Portland, 1941. Licensed in Idaho in 1942. Dr Holsinger was a member of the South Central Idaho District Medical Society.

HOSS, GLENN ARTHUR, Twin Falls. Died August 31, 1984, in Twin Falls, aged 66. Graduate of the University of Illinois College of Medicine, Chicago, 1941. Licensed in Idaho in 1941. Dr Hoss was a member of the South Central Idaho District Medical Society.

WENDLE, CORNELIUS C., Hope. Died February 20, 1984, aged 80. Graduate of Northwestern University Medical School, Chicago, 1934. Licensed in Idaho in 1934. Dr Wendle was a retired member of the Ada County Medical Society.

WYATT, JACOB E., JR, Boise. Died March 9, 1984, in Boise, aged 64. Graduate of the Creighton University School of Medicine, Omaha, 1950. Licensed in Idaho in 1952. Dr Wyatt was a member of the Ada County Medical Society.

Utah State Medical Association

DEMMAN, ANTHONY R., Helper. Died November 6, 1984, in Salt Lake City, aged 81. Graduate of the Creighton University School of Medicine, Omaha, 1931. Licensed in Utah in 1932. Dr Demman was a member of the Carbon County Medical Society.

HAWKES, GRANT ANDERSON, Salt Lake City. Died November 4, 1984, in Salt Lake City, aged 66. Graduate of the University of Utah College of Medicine, Salt Lake City, 1946. Licensed in Utah in 1947. Dr Hawkes was a member of the Salt Lake County Medical Society.

Book Reviews

The Western Journal of Medicine *does not review all books sent by publishers, although information about new books received is printed elsewhere in the journal as space permits. Prices quoted are those given by the publishers.*

BASIC & CLINICAL ENDOCRINOLOGY—Edited by Francis S. Greenspan, MD, Clinical Professor of Medicine and Radiology, Dept of Medicine, and Chief, Thyroid Clinic, University of California, San Francisco; and Peter H. Forsham, MD, Professor of Medicine and Pediatrics, University of California, San Francisco. Lange Medical Publications, Drawer L, Los Altos, CA 94022, 1983. 625 pages, $25.00 (softbound).

The editors have assembled a group of well-known basic and clinical endocrinologists, all of whom are experts in their respective fields. These authors have written an exciting textbook of endocrinology. The style of the book is geared towards facilitating clear and accurate learning. Each chapter is replete with original diagrams, charts and clinical photographs, as well as the best classical illustrations culled from other published works. The result is that each chapter presents a comprehensive overview of basic physiological and cellular mechanisms of hormone secretion and action. This is followed by well-written sections on clinical presentations, diagnosis and management of endocrine disorders. This results in a well-balanced application of basic science to clinical medicine.

The chapters cover all aspects of endocrine and metabolic physiology and disease states. They range from clear descriptions of general principles of hormone secretion and action through coverage of all the endocrine glands. The chapter on thyroid disorders stands out as a beautiful presentation of complex, basic science and clinical thyroidology. The sections explaining free thyroid hormone levels and interpretation of thyroid hormone levels in sick patients are especially clear and remove the confusion which often faces medical students and practitioners in this area. The sections on adrenal disorders, testes, sexual differentiation and development, and carbohydrate metabolism are undoubtedly superb state-of-the-art endocrinology. Each of the other chapters is written in the same clear concise and accurate style.

The book is extremely readable and will prove to be an excellent learning tool. The authors have succeeded in providing a basic and clinical endocrine text which is on the one hand comprehensive yet succinct, and on the other hand not laborious or long. This book will be welcomed by medical students, residents and all practitioners in the fields of internal medicine, gynecology and obstetrics, neurology and urology, as well as practicing and academic endocrinologists.

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* * *

ECHOCARDIOGRAPHIC DIAGNOSIS—DIFFERENTIAL DIAGNOSIS OF M-MODE AND TWO-DIMENSIONAL ECHOGRAPHIC APPEARANCES—Ivan A. D'Cruz, MD, FACC, FRCP(Edin), MRCP(Lond), Director, Echocardiography Section, and Attending Physician, Michael Reese Hospital and Medical Center, Chicago, and Associate Professor of Medicine, University of Chicago, Pritzker School of Medicine. Macmillan Publishing Company, 866 Third Ave., New York, NY 10022, 1983. 434 pages, $49.95.

Texts providing a basic foundation of echocardiographic principles have been readily accessible for a number of years; a fresh new approach being more than welcome. On reading *Echocardiographic Diagnosis,* by Ivan D'Cruz, one receives that welcome surprise.

For those accustomed to continuity in reading, D'Cruz's book may be a bit confining in style as it is organized (as advertised) with a strong emphasis on outline format. This is somewhat prerequisite since the orientation of the book is toward differential diagnosis rather than toward in-depth pathophysiologic explanations of individual disease processes where notes on imaging are sometimes a secondary consideration. *Echocardiographic Diagnosis* recapitulates the differential diagnosis approach, the technique we as physicians use every day, and thereby facilitates and fine tunes basic diagnostic principles learned elsewhere with respect to two-dimensional and M-mode appearances. There is a conspicuous absence of standard appendices of measurements present in most echocardiographic texts, although the information is included, and one may long for such a section for quick reference while perusing the text. However, this is not a basic echocardiographic reference.

Accompanying many sections on differential diagnosis is also the very nice addition of a section on common pitfalls in differential diagnosis, or common mistakes that may be made while establishing a narrower differential diagnosis. In other words, D'Cruz explains how to avoid the bugaboos in diagnosis. This, in itself, also functions as a helpful reinforcement of the preceding material learned. Nearly every important statement in D'Cruz's text is comprehensively referenced, leaving no question as to its origin or validity. Echocardiographic entities are demonstrated with excellent quality strip chart recordings and although the two-dimensional images are good, they fall victim to the slight but ever present degradation inherent in freeze-frame reproductions. In instances where the two-dimensional finding is subtle, D'Cruz does not hesitate in the timely use of diagrams to facilitate the echographic interpretation.

Finally, D'Cruz's text is a pleasure to read and its outline type organization makes learning of information easier. It will add useful information and references to the repertoire of any physician who practices echocardiography.

MARK A. DENNIS, MD
Ultrasound Instructor
University of Colorado Health Sciences Center
Denver

* * *

WHY NOT SAY IT CLEARLY. A GUIDE TO SCIENTIFIC WRITING—Lester S. King, MD. Little, Brown & Company, 34 Beacon St., Boston, MA 02106, 1978. $10.95.

This little book, written by the former senior editor of the *Journal of the American Medical Association,* is now, deservedly, in its fourth printing. There is good reason for its popularity. Dr King has sound advice not only for scientific writers but for all who want to improve their skills in expository writing.

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March 25-29—**Advanced Microsurgery Training Workshop.** UCSD. Monday-Friday. 34 hrs. Fee: $1,200. Contact: UCSD.

April 1-5—**Basic Microsurgery Training Workshop.** UCSD. Monday-Friday. 34 hrs. Fee: $1,200.

April 1-5—**12th Annual Spring Meeting of American College of Surgeons** at Hilton Hawaiian Village Hotel, and Westin Ilikai Hotel, Hawaii. Sunday-Thursday. Contact: ACS, 55 E. Erie St., Chicago, Il 60611.

April 24-26—**Postgraduate Course in General Surgery.** UCSF at Hilton Hotel, San Francisco. Wednesday-Thursday.

May 2-4—**Postgraduate Course in General Surgery.** UCSF at St. Francis Hotel, San Francisco. Thursday-Saturday. 15 hrs.

May 13-17—**Basic Microsurgery Training Workshop.** UCSD. Monday-Friday. 34 hrs. Fee: $1,200.

May 30-31—**14th Annual Neurosurgery and 8th Annual Neurosurgical Nurses Conference.** UCSF at San Francisco Hilton Hotel, San Francisco. Thursday-Friday. 15.5 hrs.

OF INTEREST TO ALL PHYSICIANS

March 20-22—**Advances and Controversies in Bronchial Asthma.** California Thoracic Society at Marriott's Santa Barbara Biltmore Hotel, Santa Barbara. Wednesday-Friday. Contact: Medical Education Director, California Thoracic Society, 424 Pendleton Way, Oakland 94621. (415) 638-5864.

March 21-22—**Current Practices in Diagnosis & Treatment of Arthritis—Connective Tissues and Musculoskeletal Diseases.** Palo Alto Medical Foundation at St. Francis Hotel, San Francisco. Thursday-Friday. 12 hrs. Contact: Palo Alto Medical Foundation, 385 Homer Ave, Palo Alto, 94301.

March 22-23—**Cancer and Sexuality Postgraduate Institute.** California Medical Association at Marriott Inn, Marina del Rey. Friday-Saturday. Contact: CMA, 44 Gough St, San Francisco 94103-1233. (415) 863-5522.

March 23—**Diabetes and Nutrition.** UCLA. Saturday. 7 hrs.

March 25-29—**Family Practice Refresher Course—1985.** UCSD at Palm Springs Spa Hotel. Monday-Friday. 30 hrs.

March 29-31—**Office Emergencies in Primary Care.** Continuing Medical Education Associates at Hotel Del Coronado, San Diego. Friday-Sunday. 18 hrs. Fee: $275. Contact: Jackie Shiller, CMEA, PO Box 84296, San Diego 92138. (619) 223-2997.

April 8-11—**Diabetes Mellitus: Modern Management Methods.** LLU at Maui Marriott, Maui. Monday-Wednesday. 16 hrs.

April 12-17—**2nd Annual Spring Conference.** Western Regional Chapters of the Society of Nuclear Medicine at Hotel Intercontinental, San Diego. Friday-Wednesday. 25 hrs. Contact: Justine Parker, PO Box 40279, San Francisco 94140. (415) 647-0722.

April 17-21—**Mountain Medicine: 1985.** UCD at North Lake Tahoe. Wednesday-Sunday.

April 24-28—**Annual Scientific Program and Postgraduate Course.** Pacific Coast Fertility Society at Caesars Palace, Las Vegas. Wednesday-Sunday. 23 hrs. Contact: Pacific Coast Fertility Society, 5820 Wilshire Blvd., #500, Los Angeles 90036. (213) 937-5514.

April 27-28—**13th Annual Family Practice Symposium.** Southern Permanente Group at Disneyland Hotel, Anaheim. Friday-Saturday. 11 hrs. Contact: Southern California Kaiser Permanente Group, 4747 Sunset Blvd, Los Angeles 90027.

May 3—**One Day Orthopaedics and Casting Procedures Workshop.** Continuing Medical Education Associates at Holiday Inn, Union Square, San Francisco. Friday. 7 hrs. Fee: $165. Contact: J. Shiller, CME Assoc., PO Box 84296, San Diego 92138. (619) 223-2997.

May 4-5—**The Father in Human Development.** San Francisco Psychoanalytic Institute at University of California, Davis. Saturday-Sunday. 10 hrs. Contact: San Francisco Psychoanalytic Institute, 2420 Sutter St., San Francisco 94115. (415) 563-5815.

May 4-11—**Applications in Preventive Medicine.** University of Arizona at California Wine Country. One Week. 24 hrs. Contact: Richard Paris, MD, PO Box 209, Sun Valley, ID 83353. (208) 788-4995.

May 5—**One Day Orthopaedics and Casting Procedures Workshop.** Continuing Medical Education Associates at Grand Hotel, Anaheim. Sunday. 7 hrs. Fee: $165. Contact: J. Shiller, CME Assoc., PO Box 84296, San Diego 92138. (619) 223-2997.

May 11-17—**San Francisco Orthopaedic Review—1985.** UCSF at Golden Gateway Holiday Inn, San Francisco. Tuesday-Sunday. 41 hrs.

May 15-17—**Child Abuse: Systems of Intervention.** UCD at Holiday Inn Holidome, Sacramento. Friday-Sunday.

May 21-24—**6th Annual Verne T. Inman Lectureship and 20th Annual Scientific Program.** UCSF at San Francisco. Tuesday-Friday. 14 hrs.

May 19-23—**Current Concepts in Primary Care: 12th Annual Family Practice Refresher Course.** UCD at Napa Valley. Sunday-Thursday.

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(Continued on Page 424)

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Pasadena	Apr. 4, 1985	Holiday Inn • 303 E. Cordova St.
Anaheim	Apr. 5, 1985	Hilton at the Park • 1855 S. Harbor Blvd.
Sacramento	Apr. 15, 1985	Sacramento Inn • 1401 Arden Way
Thousand Oaks	Apr. 15, 1985	Howard Johnsons • 75 W. Thousand Oaks Blvd.
Palo Alto	Apr. 16, 1985	Hyatt Rickeys • 4219 El Camino
Torrance	Apr. 16, 1985	Torrance Marriott • 3635 Fashion Way
San Francisco	Apr. 17, 1985	Sheraton Palace Hotel • 639 Market St.
Los Angeles	Apr. 17, 1985	Hyatt on Sunset • 8401 Sunset Blvd.
Seattle, WA	Apr. 18, 1985	Hyatt Seattle • 17001 Pacific Hwy. South
Pasadena	Apr. 18, 1985	The Pasadena Hilton • 150 S. Los Robles at Cordova St.
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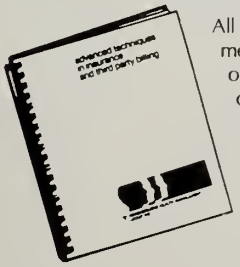

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(Continued from Page 422)

Los Angeles. Thursday. Contact: Georges M. Halpern, MD, Division of Rheumatology/Allergy, UCD.

June 5-9—**28th Annual Clinical Conference and 3rd Annual Training Institute.** Northern California Pyschotherapy Society at Asilomar, Pacific Grove. Wednesday-Sunday. 17 hrs. Contact: Northern California Psychotherapy Society, 188 Gravatt Drive, Berkeley 94705.

June 6-9—**California Society of Anesthesiologists Annual Scientific Meeting** at Hilton Hotel, San Francisco. Thursday-Sunday. 17 hrs. Contact: CSA, 100 S. Ellsworth Ave., Ste. 806, San Mateo 94401. (415) 348-1407.

June 14-16—**29th Annual Postgraduate Symposium Update 1985.** San Diego Academy of Family Physicians at Hotel Del Coronado, Coronado. Friday-Sunday. Contact: San Diego Acad. of Family Physicians, 2834 Levante St., La Costa 92008. (619) 436-0981.

June 17-22—**The UCI Family Practice Refresher Course.** UCI at Westin South Coast Plaza, Long Beach. Monday-Saturday. 58 hrs.

June 22-23—**Mullens-White Symposia: Non-Invasive Evaluation and Minimal Incision Surgery.** Stanford at Palo Alto. Saturday-Sunday.

June 29-30—**7th Annual Symposium on Toxicological Emergencies.** UCSF at Cathedral Hill Hotel, San Francisco. Saturday-Sunday. Fee: $210.

June 30—**Personality and Disease: The Emerging Field of Psychoneuro-immunology.** UCSD at University of California, Santa Barbara. Sunday. 6 hrs.

ALASKA

June 5-8—**Alaska State Medical Association Convention.** Haines. Wednesday-Saturday. Contact: ASMA, 4107 Laurel St., Anchorage 99504. (907) 562-2662.

IDAHO

March 22—**Idaho Thoracic Society—Annual Medical Symposium.** Anderson Center, Boise. 6 hrs. $20 for members; $40, nonmembers. Contact: Idaho Thoracic Society, 2621 Camas St, Boise 83705. (208) 344-6567.

July 24-27—**Idaho Medical Association Annual Meeting.** Sun Valley. Wednesday-Saturday. Contact: IMA, 407 W Bannock St, PO Box 2668, Boise 83701. (208) 344-7888.

MONTANA

April 17-19—**Internal Medicine Review.** University of Washington at Great Falls, Billings, Missoula. Wednesday-Friday. Contact: U/W School of Medicine, Div. of CME-50, Seattle, WA 98195. (206) 543-1050.

May 22-24—**Internal Medicine Review.** University of Washington at Great Falls, Billings, Missoula. Wednesday-Friday. Contact: U/W School of Medicine, Div. of CME-50, Seattle, WA 98195. (206) 543-1050.

NEW MEXICO

Information, requests for accreditation and items to be listed should be sent to the chairman of the CME Committee, New Mexico Medical Society, 303 San Mateo NE, Suite 204, Albuquerque, NM 87108 at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 266-7868.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

March 15-16—**Primary Care Orthopaedics.** Albuquerque. Friday-Saturday. AMFAC Hotel. 15 hrs. AMA Cat. I. Contact: Office of CME, UNM SOM, Albuquerque 87131. (505) 277-3942.

April 11-13—**Seventh Annual Pediatric Cardio-Pulmonary Update.** Thursday-Saturday. AMFAC Hotel. 15 hrs. AMA Cat. I. Contact: Office of CME, UNM SOM, Albuquerque 87131. (505) 277-3942.

May 1-3—**New Mexico Medical Society Annual Meeting.** Albuquerque. Wednesday-Friday. Marriott. Contact: New Mexico Medical Society, 303 San Mateo NE, Suite 204, Albuquerque 87108. (505) 266-7868.

(Continued on Page 428)

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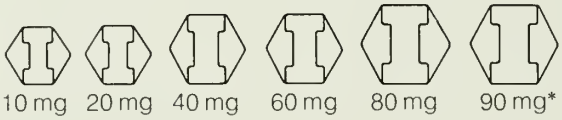

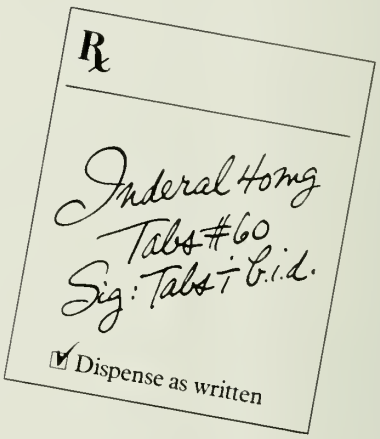

BRIEF SUMMARY (FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE CIRCULAR.)

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CONTRAINDICATIONS

INDERAL is contraindicated in 1) cardiogenic shock, 2) sinus bradycardia and greater than first degree block, 3) bronchial asthma, 4) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL.

WARNINGS

CARDIAC FAILURE. Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta blockade may precipitate more severe failure. Although beta blockers should be avoided in overt congestive heart failure, it necessary they can be used with close follow-up in patients with a history of failure who are well compensated and are receiving digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle.

IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta blockers can, in some cases, lead to cardiac failure. Therefore, at the first sign or symptom of heart failure, the patient should be digitalized and/or treated with diuretics, and the response observed closely; or INDERAL should be discontinued (gradually if possible).

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following abrupt discontinuance of INDERAL therapy. Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced over at least a few weeks and the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)—PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

MAJOR SURGERY. The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

INDERAL, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in starting and maintaining the heartbeat has also been reported with beta blockers.

DIABETES AND HYPOGLYCEMIA. Beta-adrenergic blockade may prevent the appearance of certain premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia in labile insulin-dependent diabetes. In these patients, it may be more difficult to adjust the dosage of insulin.

THYROTOXICOSIS. Beta blockade may mask certain clinical signs of hyperthyroidism. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

PRECAUTIONS

General. Propranolol should be used with caution in patients with impaired hepatic or renal function. INDERAL is not indicated for the treatment of hypertensive emergencies.

Beta-adrenoreceptor blockade can cause reduction of intraocular pressure. Patients should be told that INDERAL (propranolol hydrochloride) may interfere with the glaucoma screening test. Withdrawal may lead to a return of increased intraocular pressure.

Clinical Laboratory Tests. Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

DRUG INTERACTIONS. Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if INDERAL is administered. The added catecholamine-blocking action may produce an excessive reduction of resting sympathetic nervous activity which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility. Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In 18-month studies in both rats and mice, employing doses up to 150 mg/kg/day, there was no evidence of significant drug-induced toxicity. There were no drug-related tumorigenic effects at any of the dosage levels. Reproductive studies in animals did not show any impairment of fertility that was attributable to the drug.

Pregnancy. Pregnancy Category C. INDERAL has been shown to be embryotoxic in animal studies at doses about 10 times greater than the maximum recommended human dose.

There are no adequate and well-controlled studies in pregnant women. INDERAL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. INDERAL is excreted in human milk. Caution should be exercised when INDERAL is administered to a nursing woman.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Most adverse effects have been mild and transient and have rarely required the withdrawal of therapy.

Cardiovascular: bradycardia, congestive heart failure; intensification of AV block, hypotension, paresthesia of hands, thrombocytopenic purpura, arterial insufficiency, usually of the Raynaud type.

Central Nervous System: Lightheadedness, mental depression manifested by insomnia, lassitude, weakness, fatigue, reversible mental depression progressing to catatonia, visual disturbances, hallucinations, an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Gastrointestinal: nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis.

Allergic: pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Respiratory: bronchospasm.

Hematologic: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Auto-Immune: In extremely rare instances, systemic lupus erythematosus has been reported.

Miscellaneous: alopecia. LE-like reactions, psoriasiform rashes, dry eyes, male impotence, and Peyronie's disease have been reported rarely. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been associated with propranolol.

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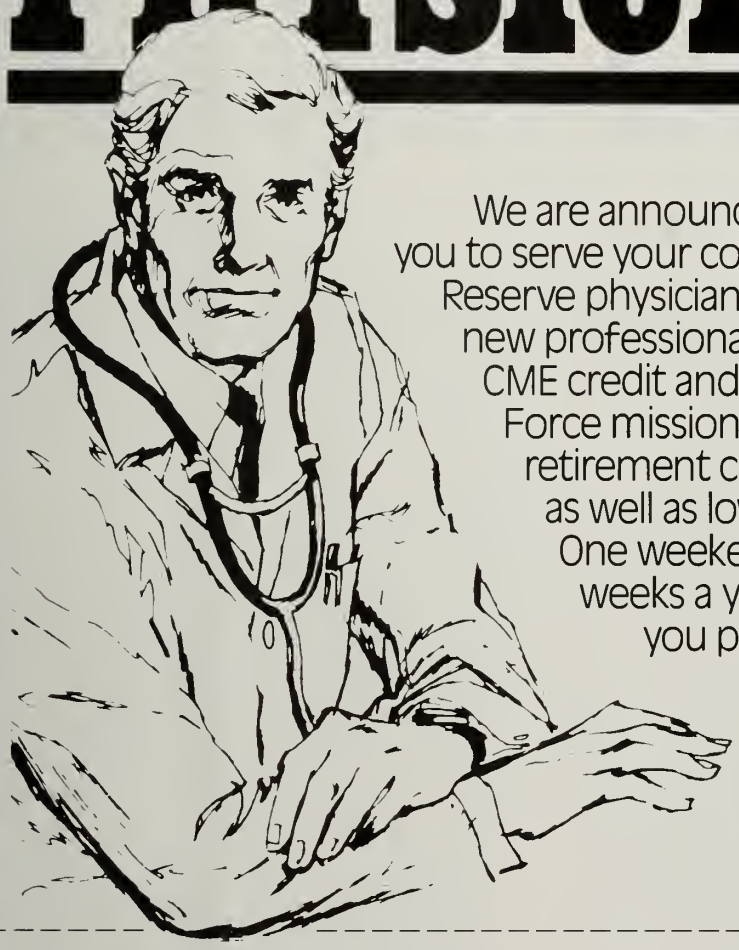
PHYSICIANS



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(Continued from Page 424)

OREGON

The following list of continuing medical offerings in the state of Oregon is compiled by the Oregon Medical Association's Council on Medical Education. If you wish to submit information regarding future postgraduate courses, please submit the information to James A. Kronenberg, Associate Executive Director, Oregon Medical Association, 5210 SW Corbett Ave., Portland, OR 97201, or phone (503) 226-1555.

MEDICAL GRAND ROUNDS

Douglas Community Hospital, 738 West Harvard Avenue, Roseburg 97470:

Every Monday, 12:30 p.m. Contact: Robert A. Driver, MD, Douglas Community Hospital, 738 West Harvard Avenue, Roseburg, OR 97470. (503) 673-6641.

Emanuel Hospital, 2801 N. Gantenbein Street, Portland 97227:

Every Friday, 8:00 a.m. to 9:00 a.m. **Medical Grand Rounds.** Contact: Philipa McClure, Emanuel Hospital, 2801 N. Gantenbein Street, Portland, OR 92227. (505) 280-3200.

Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland 97210:

Every Wednesday, 8:00 a.m. to 9:00 a.m. **Medicine Grand Rounds.** Nursing Education Building, Room 110. Contact: Department of Medicine, Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland, OR 97201. (503) 229-7454.

Providence Medical Center, 4805 NE Glisan, Portland 97213:

Every Wednesday, 8:00 a.m. **Medical Grand Rounds.** Contact: Richard Wernick, MD, Providence Medical Center, 4805 NE Glisan, Portland, OR 97213. (503) 230-6085.

Sacred Heart General Hospital, 1200 Alder Street, Eugene, OR 97440:

Every Tuesday, 8:00 a.m. to 9:00 a.m. **Medical Grand Rounds.** Hospital Auditorium. Contact: Medical Education Committee. PO Box 10905, Eugene, OR 97440.

CONTACT INFORMATION

OHSU-CME—Contact: Division of Continuing Medical Education, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8700.

Salem Hospital, 665 Winter Street SE, Salem 97301:

First and third Thursday of each month 7:15 a.m. to 8:15 a.m. **Medical Live Audit Conference.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter Street SE, Salem, OR 97301. (503) 370-5339.

Every Friday, 7:30 a.m. to 8:30 a.m. **Friday Grand Rounds.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter Street SE, Salem, OR 97301. (503) 370-5339.

St. Vincent Hospital & Medical Center, 9205 SW Barnes Road, Portland 97225:

First, third, fourth and fifth Wednesday of each month, 8:00 a.m. to 9:00 a.m. **Medical Grand Rounds.** Souther Auditorium. Contact: Bonnie Conger, Secretary to Dr Kenneth Melvin, St. Vincent Hospital & Medical Center, 9205 SW Barnes Road, Portland 97225. (503) 297-4411, Ext. 2230

Oregon Health Sciences University, Department of Psychiatry, Portland 97201:

Every Wednesday, 4:00 p.m. to 5:00 p.m. **Department of Psychiatry Grand Round Presentations.** Room 8B-60, University Hospital South, Oregon Health Sciences University. Contact: Dept. of Psychiatry, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8144.

Oregon Health Sciences University, Department of Medicine, Portland 97201:

Every Tuesday, 8:00 a.m. to 9:00 a.m. **Department of Medicine Grand Rounds.** U.H.S.-8B-60, Oregon Health Sciences University. Contact: Dept. of Medicine, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8607.

FAMILY PRACTICE GRAND ROUNDS

Every Wednesday, 11:00 a.m. to 12:00 Noon. **Family Practice Grand Rounds.** Family Practice Center, Oregon Health Sciences University, Portland. Contact: William A. Fisher, MD, Oregon Health Sciences University, Department of Family Practice, Portland, OR 97201. (503) 225-7590.

DERMATOLOGY

March 27-28—**Dermatopathology Conference.** Portland. Wednesday-Thursday. Marriott Hotel. Contact: OHSU-CME.

(Continued on Page 430)

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(Continued from Page 428)

INTERNAL MEDICINE

May 31-June 1—**Internal Medicine Update.** Portland. Friday-Saturday. Marriott Hotel. Contact: OHSU-CME.

PATHOLOGY

March 27-28—**Dermatopathology Conference.** Portland. Wednesday-Thursday. Marriott Hotel. Contact: OHSU-CME.

OF INTEREST TO ALL PHYSICIANS

April 11-12—**Sommer Memorial Lectures.** Portland. Thursday-Friday. OHSU Library Auditorium. Contact: OHSU-CME.

May 10—**Hypertension.** Portland. Friday. OHSU Library Auditorium. Contact: OHSU-CME.

May 17—**Infectious Diseases in Clinical Practice.** Portland. Friday. OHSU Library Auditorium. Contact: OHSU-CME.

May 31-June 1—**Internal Medicine Update.** Portland. Friday-Saturday. Marriott Hotel. Contact: OHSU-CME.

June 28-29—**Osteoporosis Conference.** Portland. Friday-Saturday. Red Lion Lloyd Center. Contact: OHSU-CME.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah State Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. They also must meet the definition of Utah Approved CME Credit for the purpose of medical license reregistration in Utah. Accredited institutions wishing to list AMA Category 1/Utah Approved CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, Utah 84102; or phone (801) 355-5290. For information on CME accreditation or on the CME requirements of the Utah Physicians' Licensing Board, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution or the CME office for current details.

MEDICAL GRAND ROUNDS

Each Wednesday—8:00-9:00 a.m. Alternating between University of Utah Medical Center and VA Medical Center, Salt Lake City. Contact: William D. Odell, MD, PhD, Professor and Chairman, Dept. of Internal Medicine, Univ. of Utah, (801) 581-7606.

* * *

March 18-22—**5th Annual Nutrition in Contemporary Medicine Symposium** (Sponsor: University of Utah). Monday-Friday. Park City. Fee to be announced. 29 hrs. Contact: M. Rita Thomas, MD, (801) 581-3581.

March 21-23—**Practical Neurology for Clinicians** (Sponsor: University of Utah). Thursday-Saturday. Sheraton Hotel, Salt Lake City. Fee to be announced. 18 hrs. Contact: Richard Baringer, MD, (801) 581-8664.

March 28-30—**Laser Applications in Trachaea, Bronchus.** (Sponsor: University of Utah). Thursday-Saturday. Salt Lake City Marriott. 8 hrs. Contact: Kenneth Casey, MD, (801) 581-3293.

June 7-8—**Advanced Trauma Life Support** (Sponsor: University of Utah). Friday-Saturday. Salt Lake Quality Inn, Salt Lake City. 16 hrs. $405. Contact: Kim Tanner, RN, (801) 533-6608.

SPONSORS OF COURSES—ABBREVIATIONS

AF: Arthritis Foundation, 1174 East 2700 South, Salt Lake City 84117. (801) 466-9389.

CH: Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price, UT 84501. (801) 637-4800.

CWH: Cottonwood Hospital, 5770 South 300 East, Salt Lake City 84101. (801) 262-3461.

FHP: Family Health Program/Utah, 323 South Sixth East, Salt Lake City 84102. (801) 335-1234. Contact: Kay Schultz for course information.

HAFB: Hill Air Force Hospital, Hill Air Force Base 84406. (801) 777-1262.

HCH: Holy Cross Hospital, 1045 East First South, Salt Lake City 84102. (801) 350-4744.

LDSH: Latter-Day Saints Hospital, 325 8th Avenue, Salt Lake City 84143. (801) 350-1100.

MDH: McKay-Dee Hospital Center, 3939 Harrison Blvd., Ogden 84409. (801) 399-4141.

OEH: Rocky Mountain Center for Occupational and Environmental Health, 50 North Medical Drive, Salt Lake City 84132. (801) 581-8719.

OSS: Ogden Surgical Society, PO Box 9311, Ogden 84409.

PCMC: Primary Children's Medical Center, 320 12th Ave., Salt Lake City 84103. (801) 363-1221.

SHCC: Shriners Hospital for Crippled Children, Intermountain Unit, Fairfax Ave. at Virginia St., Salt Lake City 84103. (801) 532-5307.

SLSC: Salt Lake Surgical Center, 617 East 3900 South, Salt Lake City 84117. (801) 261-3141.

UAFP: Utah Academy of Family Physicians, 1146 Westminster Ave., Salt Lake City 84105. (801) 466-9478.

UUMC: University of Utah Medical Center, 50 North Medical Drive, Salt Lake City 84132. (801) 581-2258.

USMA: Utah State Medical Association, 540 East Fifth South, Salt Lake City 84102. (801) 355-7477.

UVH: Utah Valley Hospital, 1034 North Fifth West, Provo 84601. (801) 373-7850.

VAMC: Veterans Administration Medical Center, 500 Foothill Drive, Salt Lake City 84148. (801) 582-1565.

July 14-19—**Summer Update in Clinical Microbiology and Immunology** (Sponsor: University of Utah). Sunday-Friday. Jackson Hole, American Snow King. 23 hrs. Contact: John Matsen, MD, (801) 581-7480.

WASHINGTON

This listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121; or phone (206) 623-4801.

Brochures and Registration Forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

March 15—**Soft Tissue Surgery.** Seattle. Friday. Contact: VMMC.

March 15—**Small Computers in Medical Practice.** Seattle. Friday. Riverton Hospital. Contact: U/W.

March 16-23—(HAWAII) **Drug Therapy.** Maui. Saturday-Saturday. Royal Lahaina. Contact: U/W.

March 19—**Epilepsy.** Seattle. Tuesday. Ballard Hospital. Contact: U/W.

March 21-22—**Advances in Internal Medicine.** Seattle. Thursday-Friday. U/W HUB. Contact: U/W.

March 22—**Medicine in Mainland China.** Seattle. Friday. Riverton Hospital. Contact: U/W.

March 23—**Magnetic Resonance Imaging.** Seattle. Saturday. U/W South Campus Center. Contact: U/W.

March 23-30—(HAWAII) **Vascular Surgery.** Maui. Saturday-Saturday. Royal Lahaina. Contact: U/W.

March 26—**Alzheimer's Disease.** Auburn. Tuesday. Auburn General Hospital. Contact: U/W.

March 29—**Convulsing and Floppy Kids.** Seattle. Friday. Riverton Hospital. Contact: U/W.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

CME PIERCE COUNTY—Contact: Mrs Maxine Bailey, Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 223-6898.

Books Received

Books received by THE WESTERN JOURNAL OF MEDICINE *are acknowledged in this column. Selections will be made for more extensive review in the interest of readers as space permits.*

CONTROVERSIES IN NEPHROLOGY AND HYPERTENSION—Edited by Robert G Narins, MD, Professor of Medicine and Chief, Renal Section, Temple University Health Sciences Center, Philadelphia. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1984. 605 pages, $60.00.

DO-IT-YOURSELF MEDICAL TESTING—Cathey Pinckney and Edward R. Pinckney, MD. Facts on File Publications, 460 Park Ave S, New York, NY 10016, 1983. 290 pages, $7.95 (paperback).

INTRODUCTION TO LABORATORY HEMATOLOGY AND HEMATOPATHOLOGY—Harold R. Schumacher, MD, Head, Hematopathology, Naval Hospital, and Professor of Pathology and Medicine, Uniformed Services University of the Health Sciences, Bethesda, Maryland, and Clinical Professor of Medicine and Pathology, Georgetown University Medical Center, Washington, DC; David F. Garvin, MD, Head, Department of Laboratory Medicine, Naval Hospital, and Associate Professor of Pathology, Uniformed Services University of the Health Sciences, Bethesda, Maryland, and Douglas A. Triplett, MD, Director of Hematology, Ball Memorial Hospital, and Professor of Pathology and Assistant Dean, Muncie Center for Medical Education, Indiana University School of Medicine, Muncie. Alan R. Liss, Inc, 150 Fifth Ave, New York, NY 10011, 1984. 599 pages, $49.50.

MUTILATING INJURIES OF THE HAND: Second Edition—Edited by D. A. Campbell Reid and R. Tubiana. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1984. 212 pages, $55.00.

OCCUPATIONAL LUNG DISEASE—Edited by J. Bernard L. Gee, MD, Professor of Medicine, Yale University School of Medicine, New Haven, Conn. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1984. 254 pages, $32.50.

PRETERM BIRTH: CAUSES, PREVENTION, AND MANAGEMENT—Edited by Fritz Fuchs, MD, Professor of Obstetrics and Gynecology, Cornell University Medical College, and Attending Obstetrician and Gynecologist, The New York Hospital, New York, and Phillip G. Stubblefield, MD, Associate Professor of Obstetrics and Gynecology, Harvard Medical School, Boston, and Chairman, Department of Obstetrics and Gynecology, Mt Auburn Hospital, Cambridge, Mass. Macmillan Publishing Co, 866 Third Ave, New York, NY 10022, 1984. 376 pages, $48.00.

TOXIC EMERGENCIES—Volume 5 of CLINICS IN EMERGENCY MEDICINE—Edited by William Hanson, Jr, MD, Clinical Associate Professor of Medicine, Department of Emergency Services, Hospital of the University of Pennsylvania, Philadelphia. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1984. 319 pages, $35.00.

TREATING TYPE A BEHAVIOR—AND YOUR HEALTH—Meyer Friedman, MD, Director, and Diane Ulmer, RN, MS, Supervising Director, Recurrent Coronary Prevention Project at the Harold Brunn Institute of Mount Zion Hospital and Medical Center, San Francisco. Alfred A. Knopf, 201 E 50th St, New York, NY 10022, 1984; distributed by Random House, Inc, New York City. 285 pages, $15.95.

TROPICAL MICROBIOLOGY—D. G. Montefiore, OBE, MA, MD(Cambridge), FRCPath(Nig), FWACP(Path), DipBact(Lond), Professor of Medical Microbiology and Deputy Provost, College of Medicine; K. O. Alausa, BMedSci, MD(Ibadan), DipBact(Manchester), MPH(Harvard), MRCPath, FMCPath(Nig), FWACP(Path), Professor of Epidemiology and Community Health, University of Ilorin, and O. Tomori, DVM, PhD, MRCPath, Reader, Department of Virology, University of Ibadan, Nigeria. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1984. 341 pages, $14.00 (paperback).

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THE DIABETIC'S BRAND-NAME FOOD EXCHANGE HANDBOOK—Andrea Barrett. Running Press Book Publishers, 125 South 22nd Street, Philadelphia, PA 19103, 1984. 175 pages, $14.95 plus $1.00 postage.

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GASTROINTESTINAL RADIOLOGY—PERFORMING AND INTERPRETING FLUOROSCOPIC EXAMINATIONS—David W. Gelfand, MD, Professor and Chief of Gastrointestinal Radiology, Dept of Radiology, Bowman Gray School of Medicine, Wake Forest University, Winston-Salem, NC. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1984. 347 pages, $60.

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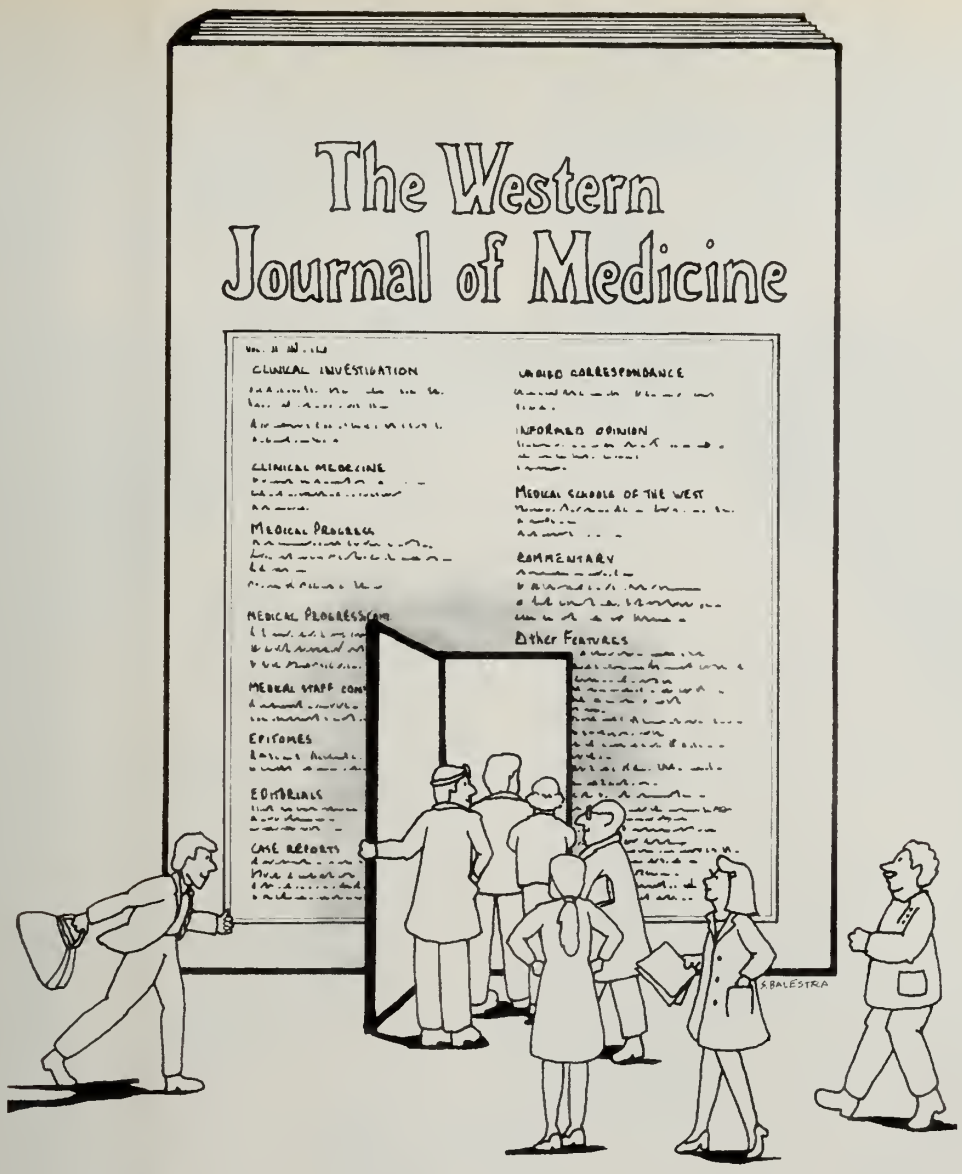

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Pamphlets, Monographs or Books With No Given Author

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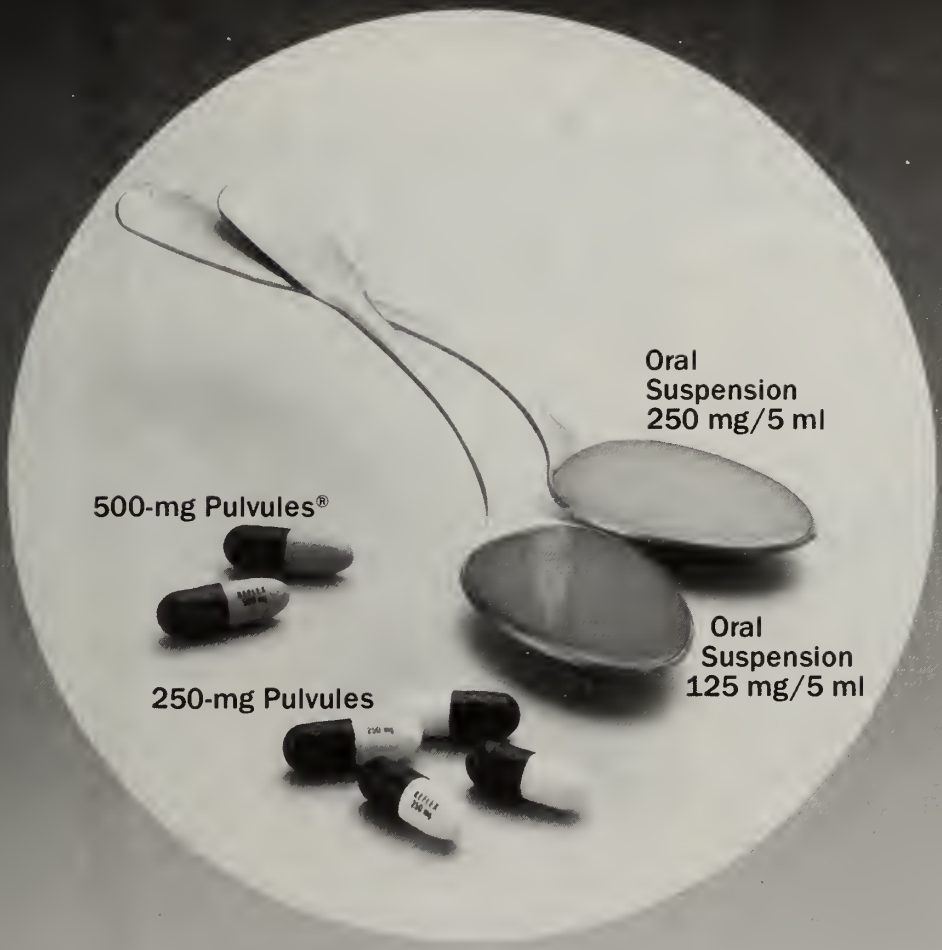

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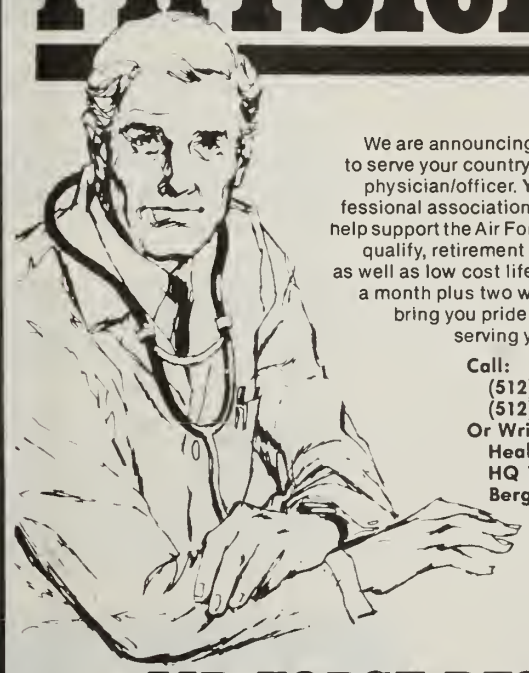

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Arizona Medical Association, Inc.—810 W. Bethany Home Rd., Phoenix 85013. (602) 246-8901. Annual Meeting: April 26-27, 1985, The Cottonwoods, Scottsdale.

California Medical Association—44 Gough St., San Francisco 94103. (415) 863-5522. Annual Meeting: March 8-13, 1985, Town and County, San Diego.

Colorado Medical Society—6825 E. Tennessee, Bldg. 2, Suite 500, Denver 80224. (303) 321-8590. Annual Meeting: September 11-14, 1985, Broadmoor, Colorado Springs.

Hawaii Medical Association—320 Ward Ave., Suite 200, Honolulu 96814. (808) 536-7702. Annual Meeting: October 12-14, 1985, Kona Surf Hotel, Kona.

Idaho Medical Association—407 W. Bannock St., PO Box 2668, Boise 83701. (208) 344-7888. Annual Meeting: July 24-27, 1985, Sun Valley.

Montana Medical Association—2012 11th Ave., Suite 12, Helena 59601. (406) 443-4000. Annual Meeting: October 3-5, 1985, Outlaw Inn, Kalispell.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: May 9-12, 1985, Hyatt, Lake Tahoe.

New Mexico Medical Society—303 San Mateo NE, Suite 204, Albuquerque 87108. (505) 266-7868. Annual Meeting: May 1-3, 1985, Marriott, Albuquerque.

Oregon Medical Association—5210 S.W. Corbett Ave., Portland 97201. (503) 226-1555. Annual Meeting: (House of Delegates only): April 26-28, 1985, Ashland Hills Inn, Ashland.

Utah State Medical Association—540 East Fifth South, Salt Lake City 84102. (801) 355-7477. Annual Meeting: September 26-27, 1985. Hotel Utah, Salt Lake City.

Washington State Medical Association—900 United Airlines Bldg., 2033 6th Ave., Seattle 98121. (206) 623-4801. Annual Meeting: September 19-22, 1985, Jantzen Beach.

Wyoming Medical Society—P.O. Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. Annual Meeting: June 23-26, 1985, Jackson Lake Lodge, Moran.

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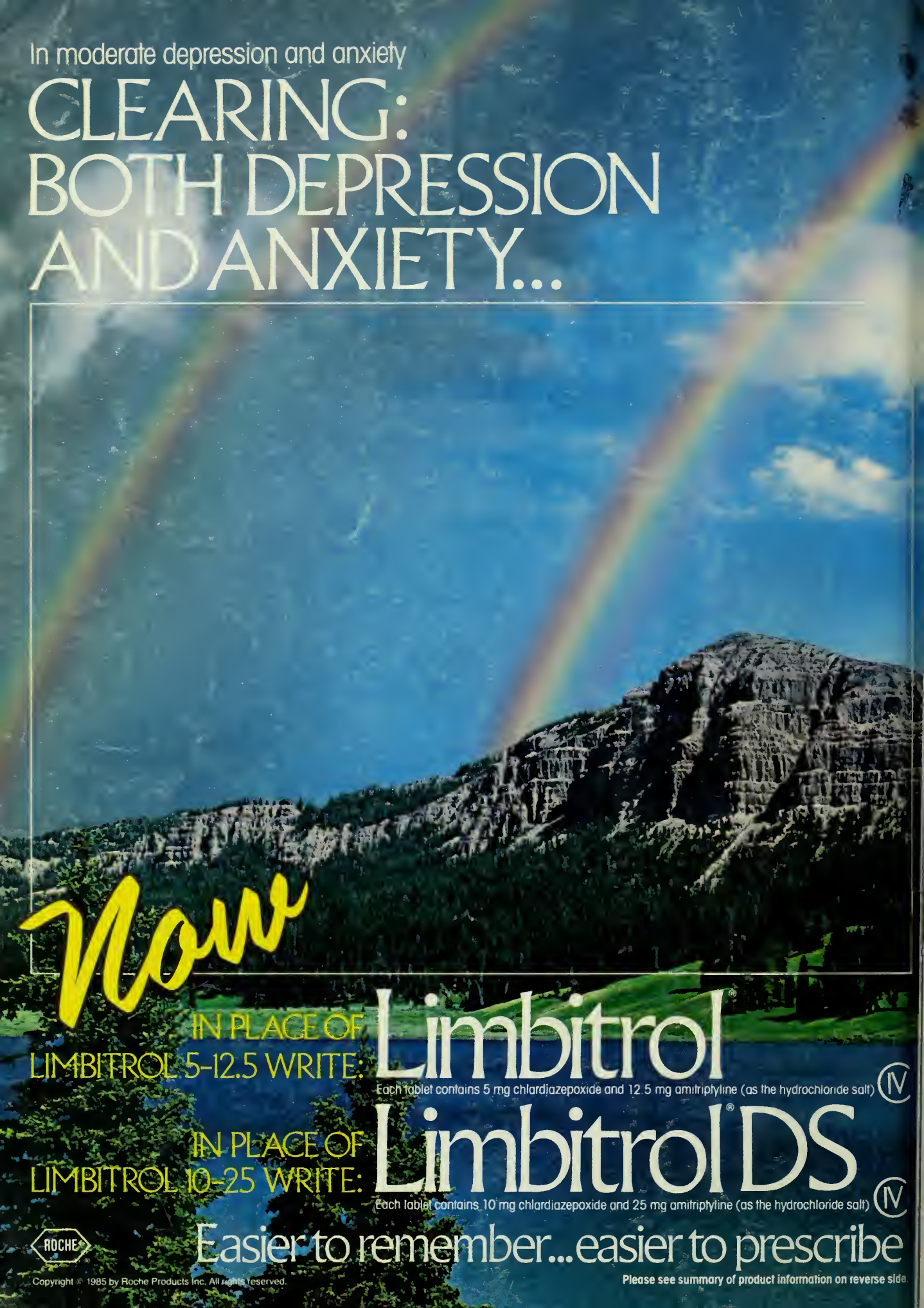
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Affiliated Clinical Investigation Societies: the Western Association of Physicians; the Western Society for Clinical Investigation; the Western Section, American Federation for Clinical Research; the Western Society for Pediatric Research; the Western Region, Society for Investigative Dermatology.

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See next page for references and summary of product information.

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References: 1. Kales J *et al: Clin Pharmacol Ther* 12:691-697, Jul-Aug 1971. 2. Kales A *et al: Clin Pharmacol Ther* 18:356-363, Sep 1975. 3. Kales A *et al: Clin Pharmacol Ther* 19:576-583, May 1976. 4. Kales A *et al: Clin Pharmacol Ther* 32:781-788, Dec 1982. 5. Frost JD Jr, DeLucchi MR: *J Am Geriatr Soc* 27:541-546, Dec 1979. 6. Kales A, Kales JD: *J Clin Pharmacol* 3:140-150, Apr 1983. 7. Greenblatt DJ, Allen MD, Shader RI: *Clin Pharmacol Ther* 21:355-361, Mar 1977. 8. Zimmerman AM: *Curr Ther Res* 13:18-22, Jan 1971. 9. Amrein R *et al: Drugs Exp Clin Res* 9(1):85-99, 1983. 10. Monti JM: *Methods Find Exp Clin Pharmacol* 3:303-326, May 1981. 11. Greenblatt DJ *et al: Sleep* 5(Suppl 1):S18-S27, 1982. 12. Kales A *et al: Pharmacology* 26:121-137, 1983.

DALMANE® Ⓥ
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Before prescribing, please consult complete product information, a summary of which follows:

Indications: Effective in all types of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings and/or early morning awakening; in patients with recurring insomnia or poor sleeping habits; in acute or chronic medical situations requiring restful sleep. Objective sleep laboratory data have shown effectiveness for at least 28 consecutive nights of administration. Since insomnia is often transient and intermittent, prolonged administration is generally not necessary or recommended. Repeated therapy should only be undertaken with appropriate patient evaluation.

Contraindications: Known hypersensitivity to flurazepam HCl; pregnancy. Benzodiazepines may cause fetal damage when administered during pregnancy. Several studies suggest an increased risk of congenital malformations associated with benzodiazepine use during the first trimester. Warn patients of the potential risks to the fetus should the possibility of becoming pregnant exist while receiving flurazepam. Instruct patient to discontinue drug prior to becoming pregnant. Consider the possibility of pregnancy prior to instituting therapy.

Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. An additive effect may occur if alcohol is consumed the day following use for nighttime sedation. This potential may exist for several days following discontinuation. Caution against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). Potential impairment of performance of such activities may occur the day following ingestion. Not recommended for use in persons under 15 years of age. Though physical and psychological dependence have not been reported on recommended doses, abrupt discontinuation should be avoided with gradual tapering of dosage for those patients on medication for a prolonged period of time. Use caution in administering to addiction-prone individuals or those who might increase dosage.

Precautions: In elderly and debilitated patients, it is recommended that the dosage be limited to 15 mg to reduce risk of oversedation, dizziness, confusion and/or ataxia. Consider potential additive effects with other hypnotics or CNS depressants. Employ usual precautions in severely depressed patients, or in those with latent depression or suicidal tendencies, or in those with impaired renal or hepatic function.

Adverse Reactions: Dizziness, drowsiness, lightheadedness, staggering, ataxia and falling have occurred, particularly in elderly or debilitated patients. Severe sedation, lethargy, disorientation and coma, probably indicative of drug intolerance or overdosage, have been reported. Also reported: headache, heartburn, upset stomach, nausea, vomiting, diarrhea, constipation, GI pain, nervousness, talkativeness, apprehension, irritability, weakness, palpitations, chest pains, body and joint pains and GU complaints. There have also been rare occurrences of leukopenia, granulocytopenia, sweating, flushes, difficulty in focusing, blurred vision, burning eyes, faintness, hypotension, shortness of breath, pruritus, skin rash, dry mouth, bitter taste, excessive salivation, anorexia, euphoria, depression, slurred speech, confusion, restlessness, hallucinations, and elevated SGOT, SGPT, total and direct bilirubins, and alkaline phosphatase; and paradoxical reactions, *e.g.*, excitement, stimulation and hyperactivity.

Dosage: Individualize for maximum beneficial effect. *Adults:* 30 mg usual dosage; 15 mg may suffice in some patients. *Elderly or debilitated patients:* 15 mg recommended initially until response is determined.

Supplied: Capsules containing 15 mg or 30 mg flurazepam HCl.

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Please consult full prescribing information before use. A summary follows:

INDICATIONS AND USAGE: SORBITRATE (isosorbide dinitrate) is indicated for the treatment and prevention of angina pectoris. All dosage forms of isosorbide dinitrate may be used prophylactically to decrease frequency and severity of anginal attacks and can be expected to decrease the need for sublingual nitroglycerin.

The sublingual and chewable forms of the drug are indicated for acute prophylaxis of angina pectoris when taken a few minutes before situations likely to provoke anginal attacks. Because of a slower onset of effect, the oral forms of isosorbide dinitrate are not indicated for acute prophylaxis.

CONTRAINDICATIONS: SORBITRATE is contraindicated in patients who have shown purported hypersensitivity or idiosyncrasy to it or other nitrates or nitrites. Epinephrine and related compounds are ineffective in reversing the severe hypotensive events associated with overdose and are contraindicated in this situation.

WARNINGS: The benefits of SORBITRATE during the early days of an acute myocardial infarction have not been established. If one elects to use organic nitrates in early infarction, hemodynamic monitoring and frequent clinical assessment should be used because of the potential deleterious effects of hypotension.

PRECAUTIONS: General: Severe hypotensive response, particularly with upright posture, may occur with even small doses of SORBITRATE. The drug should therefore be used with caution in subjects who may have blood volume depletion from diuretic therapy or in subjects who have low systolic blood pressure (eg, below 90 mmHg). Paradoxical bradycardia and increased angina pectoris may accompany nitrate-induced hypotension. Nitrate therapy may aggravate the angina caused by hypertrophic cardiomyopathy.

Marked symptomatic, orthostatic hypotension has been reported when calcium channel blockers and organic nitrates were used in combination. Dose adjustment of either class of agents may be necessary.

Tolerance to this drug and cross-tolerance to other nitrates and nitrites may occur. Tolerance to the vascular and antianginal effects of isosorbide dinitrate or nitroglycerin has been demonstrated in clinical trials, experience through occupational exposure, and in isolated tissue experiments in the laboratory. The importance of tolerance to the appropriate use of isosorbide dinitrate in the management of patients with angina pectoris has not been determined. However, one clinical trial using treadmill exercise tolerance (as an end point) found an 8-hour duration of action of oral isosorbide dinitrate following the first dose (after a 2-week placebo washout) and only a 2-hour duration of effect of the same dose after 1 week of repetitive dosing at conventional dosing intervals. On the other hand, several trials have been able to differentiate isosorbide dinitrate from placebo after 4 weeks of therapy and, in open trials, an effect seems detectable for as long as several months.

Tolerance clearly occurs in industrial workers continuously exposed to nitroglycerin. Moreover, physical dependence also occurs since chest pain, acute myocardial infarction, and even sudden death have occurred during temporary withdrawal of nitroglycerin from the workers. In clinical trials in angina patients, there are reports of anginal attacks being more easily provoked and of rebound in the hemodynamic effects soon after nitrate withdrawal. The relative importance of these observations to the routine, clinical use of isosorbide dinitrate is not known. However, it seems prudent to gradually withdraw patients from isosorbide dinitrate when the therapy is being terminated, rather than stopping the drug abruptly.

Information for Patients: Headache may occur during initial therapy with SORBITRATE. Headache is usually relieved by the use of standard headache remedies or by lowering the dose and tends to disappear after the first week or two of use.

Drug Interactions: Alcohol may enhance any marked sensitivity to the hypotensive effect of nitrates.

Isosorbide dinitrate acts directly on vascular smooth muscle, therefore, any other agent that depends on vascular smooth muscle as the final common path can be expected to have decreased or increased effect depending on the agent.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No long-term studies in animals have been performed to evaluate the carcinogenic potential of this drug. A modified two-litter reproduction study in rats fed isosorbide dinitrate at 25 or 100 mg/kg/day did not reveal any effects on fertility or gestation or any remarkable gross pathology in any parent or offspring fed isosorbide dinitrate as compared with rats fed a basal-controlled diet.

Pregnancy Category C: Isosorbide dinitrate has been shown to cause a dose-related increase in embryotoxicity (increase in mummified pups) in rabbits at oral doses 35 and 150 times the maximum recommended human daily dose. There are no adequate and well-controlled studies in pregnant women. SORBITRATE should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when SORBITRATE is administered to a nursing woman.

Pediatric Use: The safety and effectiveness of SORBITRATE in children has not been established.

ADVERSE REACTIONS: Adverse reactions, particularly headache and hypotension, are dose-related. In clinical trials at various doses, the following have been observed.

Headache is the most common (reported incidence varies widely, apparently being dose-related, with an average occurrence of about 25%) adverse reaction and may be severe and persistent. Cutaneous vasodilation with flushing may occur. Transient episodes of dizziness and weakness, as well as other signs of cerebral ischemia associated with postural hypotension, may occasionally develop (the incidence of reported symptomatic hypotension ranges from 2% to 36%). An occasional individual will exhibit marked sensitivity to the hypotensive effects of nitrates and severe responses (nausea, vomiting, weakness, restlessness, pallor, perspiration, and collapse) may occur even with the usual therapeutic dose. Drug rash and/or exfoliative dermatitis may occasionally occur. Nausea and vomiting appear to be uncommon. Case reports of clinically significant methemoglobinemia are rare at conventional doses of organic nitrates. The formation of methemoglobin is dose-related and, in the case of genetic abnormalities of hemoglobin that favor methemoglobin formation, even conventional doses of organic nitrate could produce harmful concentrations of methemoglobin.

DOSAGE AND ADMINISTRATION: For the treatment of angina pectoris, the usual starting dose for sublingual SORBITRATE is 2.5 to 5 mg; for chewable tablets, 5 mg; for oral (swallowed) tablets, 5 to 20 mg, and for controlled-release forms, 40 mg.

SORBITRATE should be titrated upward until angina is relieved or side effects limit the dose. In ambulatory patients, the magnitude of the incremental dose increase should be guided by measurements of standing blood pressure.

The initial dosage of sublingual or chewable SORBITRATE for prophylactic therapy in angina pectoris patients is generally 5 or 10 mg every 2 to 3 hours. Adequate controlled clinical studies demonstrating the effectiveness of chronic maintenance therapy with these dosage forms have not been reported.

SORBITRATE in oral doses of 10 to 40 mg given every 6 hours or in oral controlled-release doses of 40 to 80 mg given every 8 to 12 hours is generally recommended. The extent to which development of tolerance should modify the dosage program has not been defined. *The oral controlled-release forms of isosorbide dinitrate should not be chewed.*

DOSAGE FORMS AVAILABLE: Sublingual Tablets (2.5, 5, 10 mg); Chewable Tablets (5, 10 mg); Oral Tablets (5, 10, 20, 30, 40 mg); Sustained Action Tablets (40 mg).

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See previous page for brief summary of prescribing information.

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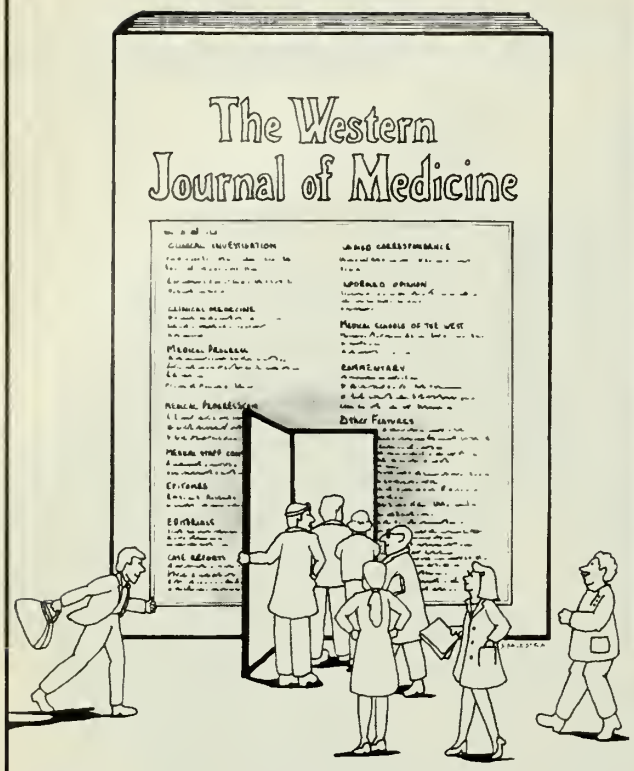

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(Continued from adjacent page)

Nursing Mothers: Captopril is secreted in human milk. Exercise caution when administering captopril to a nursing woman, and, in general, nursing should be interrupted.

Pediatric Use: Safety and effectiveness in children have not been established although there is limited experience with use of captopril in children from 2 months to 15 years of age. Dosage, on a weight basis, was comparable to that used in adults. Captopril should be used in children only if other measures for controlling blood pressure have not been effective.

ADVERSE REACTIONS: Reported incidences are based on clinical trials involving about 4000 patients.

Renal—One to 2 of 100 patients developed proteinuria (see WARNINGS). Renal insufficiency, renal failure, polyuria, oliguria, and urinary frequency in 1 to 2 of 1000 patients.

Hematologic—Neutropenia/agranulocytosis occurred in about 0.3% of captopril treated patients (see WARNINGS). Two of these patients developed sepsis and died.

Dermatologic—Rash (usually mild, maculopapular, rarely urticarial), often with pruritus and sometimes with fever and eosinophilia, in about 10 of 100 patients, usually during the 1st 4 weeks of therapy. Pruritus, without rash, in about 2 of 100 patients. A reversible associated pemphigoid-like lesion, and photosensitivity have also been reported. Angioedema of the face, mucous membranes of the mouth, or of the extremities in about 1 of 100 patients—reversible on discontinuance of captopril therapy. One case of laryngeal edema reported. Flushing or pallor in 2 to 5 of 1000 patients.

Cardiovascular—Hypotension in about 2 of 100 patients. See WARNINGS (Hypotension) and PRECAUTIONS (Drug Interactions) for discussion of hypotension on initiation of captopril therapy. Tachycardia, chest pain, and palpitations each in about 1 of 100 patients. Angina pectoris, myocardial infarction, Raynaud's syndrome, and congestive heart failure each in 2 to 3 of 1000 patients.

Dysgeusia—About 7 of 100 patients developed a diminution or loss of taste perception; taste impairment is reversible and usually self-limited even with continued drug use (2 to 3 months). Gastric irritation, abdominal pain, nausea, vomiting, diarrhea, anorexia, constipation, aphthous ulcers, peptic ulcer, dizziness, headache, malaise, fatigue, insomnia, dry mouth, dyspnea, and paresthesias reported in about 0.5 to 2% of patients but did not appear at increased frequency compared to placebo or other treatments used in controlled trials.

Altered Laboratory Findings: Elevations of liver enzymes in a few patients although no causal relationship has been established. Rarely cholestatic jaundice and hepatocellular injury with secondary cholestasis have been reported. A transient elevation of BUN and serum creatinine may occur, especially in volume-depleted or renovascular hypertensive patients. In instances of rapid reduction of longstanding or severely elevated blood pressure, the glomerular filtration rate may decrease transiently, also resulting in transient rises in serum creatinine and BUN. Small increases in serum potassium concentration frequently occur, especially in patients with renal impairment (see PRECAUTIONS).

OVERDOSAGE: Primary concern in correction of hypotension. Volume expansion with an I.V. infusion of normal saline is the treatment of choice for restoration of blood pressure. Captopril may be removed from the general circulation by hemodialysis.

DOSAGE AND ADMINISTRATION: CAPOTEN should be taken one hour before meals. Dosage must be individualized; see DOSAGE AND ADMINISTRATION section of package insert for detailed information regarding dosage in hypertension and in heart failure. Because CAPOTEN (captopril) is excreted primarily by the kidneys, dosage adjustments are recommended for patients with impaired renal function. **Consult package insert before prescribing CAPOTEN (captopril).**

HOW SUPPLIED: Available in tablets of 25, 50, and 100 mg in bottles of 100, and in UNIMATIC® unit-dose packs of 100 tablets.

SQUIBB

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ACE* INHIBITOR

Capoten®
(captopril tablets)

Precautionary Guidelines

CAPOTEN has been associated with the development of neutropenia/agranulocytosis (0.3% of 4,000 patients) or proteinuria (1.2% of 4,000 patients).† These serious side effects are more likely to occur in patients with predisposing conditions, such as renal impairment or autoimmune disease, or in patients receiving therapy known to suppress the autoimmune response.

The following precautionary guidelines are recommended for all patients receiving CAPOTEN:

☐ Obtain urinary protein level estimates prior to initiating therapy, at monthly intervals for the first nine months of treatment, and periodically thereafter.

☐ Obtain WBC counts at the initiation of therapy, at two-week intervals for the first three months of treatment, and periodically thereafter.

☐ Carefully review the WARNINGS and ADVERSE REACTIONS sections in the complete prescribing information, with particular attention to the patient at increased risk.

☐ The most frequently occurring adverse reactions are skin rash and taste alteration; both effects are generally mild, reversible, or self-limited.

*Angiotensin Converting Enzyme

†Please see the following brief summary of prescribing information for INDICATIONS AND USAGE, WARNINGS, and ADVERSE REACTIONS.

Reference: 1. Market Measures Inc.: Treatment of Hypertension V, February 1983.

CAPOTEN® TABLETS
Captopril Tablets

INDICATIONS: Hypertension—Because serious adverse effects have been reported (see WARNINGS), CAPOTEN is indicated for treatment of hypertensive patients who on multidrug regimens have either failed to respond satisfactorily or developed unacceptable side effects.

Heart Failure: CAPOTEN (captopril) is indicated in patients with heart failure who have not responded adequately to or cannot be controlled by conventional diuretic and digitalis therapy. CAPOTEN is to be used with diuretics and digitalis.

WARNINGS: Proteinuria—Total urinary proteins >1 g/day were seen in 1.2% of patients on captopril; the nephrotic syndrome occurred in about ¼th of these cases. About 60% of affected patients had evidence of prior renal disease; the remainder had no known renal dysfunction. In most cases, proteinuria subsided or cleared within 6 months whether or not captopril was continued. The BUN and creatinine were seldom altered in proteinuric patients.

Membranous glomerulopathy was found in nearly all the proteinuric patients on captopril who were biopsied and may be drug related. Most cases of proteinuria occurred by the 8th month of therapy. Patients should have urinary protein estimates (dip-stick on 1st morning urine, or quantitative 24-hr urine—the latter provides greater precision when proteinuria is persistent and/or at low levels) before therapy, at approx. monthly intervals for the 1st 9 months of therapy, and periodically thereafter. For patients who develop proteinuria >1 g/day, or increasing proteinuria, the benefits and risks of continuing captopril should be evaluated.

Neutropenia/Agranulocytosis—Neutropenia (<300/mm³) associated with myeloid hypoplasia (probably drug related) occurred in about 0.3% of captopril treated patients. About half of the neutropenic patients developed systemic or oral cavity infections or other features of agranulocytosis. Most of the neutropenic patients had severe hypertension and renal function impairment; about half had systemic lupus erythematosus (SLE), or another autoimmune/collagen disorder; multiple concomitant drug therapy was common, including immunosuppressive therapy in a few cases. Daily doses of captopril in the leukopenic patients were relatively high, particularly in view of their diminished renal function. The neutropenia appeared 3 to 12 weeks after starting captopril; it developed relatively slowly, taking 10 to 30 days to have white blood count fall to its nadir; neutrophils returned to normal in about 2 weeks (other than 2 patients who died of sepsis).

Use captopril with caution in patients with impaired renal function, serious autoimmune disease (particularly SLE), or who are exposed to other drugs known to affect the white cells or immune response. In patients at particular risk (as noted above), perform white blood cell and differential counts prior to therapy, at about 2-week intervals for about the 1st 3 months of therapy, and periodically thereafter.

The risk of neutropenia in patients who are less seriously ill or who receive lower dosages appears to be smaller. In these patients white blood cell counts should be performed every 2 weeks for the 1st 3 months of therapy, and periodically thereafter. Perform differential counts when leukocytes are <4000/mm³ or the pretherapy white count is halved. All patients treated with captopril should be told to report any signs of infection (e.g., sore throat; fever); if infection is suspected, perform counts without delay. Since discontinuation of captopril and other drugs has generally led to prompt return of the white count to normal, upon confirmation of neutropenia (neutrophil count <1000/mm³) withdraw captopril and closely follow the patient's course.

Hypotension—Excessive hypotension was rarely seen in hypertensive patients but is a possibility in severely salt/volume-depleted persons such as those treated vigorously with diuretics (see PRECAUTIONS [Drug Interactions]).

In heart failure, where blood pressure was either normal or low, transient decreases in blood pressure >20% were recorded in about ½ the patients. This transient hypotension may occur after any of the first several doses and is usually well tolerated, although rarely it has been associated with arrhythmia or conduction defects. A starting dose of 6.25 or 12.5 mg tid may minimize the hypotensive effect. Patients should be followed closely for the first 2 weeks of treatment and whenever the dose of captopril and/or diuretic is increased.

BECAUSE OF THE POTENTIAL FALL IN BLOOD PRESSURE IN THESE PATIENTS, THERAPY SHOULD BE STARTED UNDER VERY CLOSE MEDICAL SUPERVISION.

PRECAUTION: General: *Impaired Renal Function,* Hypertension—Some hypertensive patients with renal disease, particularly those with severe renal artery stenosis, have developed increases in BUN and serum creatinine. It may be necessary to reduce captopril dosage and/or discontinue diuretic. For some of these patients, normalization of blood pressure and maintenance of adequate renal perfusion may not be possible. Heart Failure—About 20% of patients develop stable elevations of BUN and serum creatinine >20% above normal or baseline upon long-term treatment. Less than 5% of patients, generally with severe preexisting renal disease, required discontinuation due to progressively increasing creatinine. See DOSAGE AND ADMINISTRATION, ADVERSE REACTIONS [Altered Laboratory Findings]. *Valvular Stenosis*—A theoretical concern, for risk of decreased coronary perfusion, has been noted regarding vasodilator treatment in patients with aortic stenosis, due to decreased afterload reduction.

Surgery/Anesthesia—If hypotension occurs during major surgery or anesthesia, and is considered due to the effects of captopril, it is correctable by volume expansion.

Drug Interactions: *Hypotension. Patients on Diuretic Therapy*—Precipitous reduction of blood pressure may occasionally occur within the 1st 3 hours after administration of the initial captopril dose in patients on diuretics, especially those recently placed on diuretics and those on severe dietary salt restriction or dialysis. This possibility can be minimized by either discontinuing the diuretic or increasing the salt intake about 1 week prior to initiation of captopril therapy. Alternatively, provide medical supervision for at least 3 hours after the initial dose in hypertensive patients.

Agents Having Vasodilator Activity: In heart failure patients vasodilators should be administered with caution.

Agents Causing Renin Release—Captopril's effect will be augmented by antihypertensive agents that cause renin release.

Agents Affecting Sympathetic Activity—The sympathetic nervous system may be especially important in supporting blood pressure in patients receiving captopril alone or with diuretics. Beta-adrenergic blocking drugs add some further antihypertensive effect to captopril, but the overall response is less than additive. Therefore, use agents affecting sympathetic activity (e.g., ganglionic blocking agents or adrenergic neuron blocking agents) with caution.

Agents Increasing Serum Potassium—Give potassium-sparing diuretics or potassium supplements only for documented hypokalemia, and then with caution, since they may lead to a significant increase of serum potassium.

Drug/Laboratory Test Interaction: Captopril may cause a false-positive urine test for acetone.

Carcinogenesis, Mutagenesis, and Impairment of Fertility: Two-year studies with doses of 50 to 1350 mg/kg/day in mice and rats failed to show any evidence of carcinogenic potential. Studies in rats have revealed no impairment of fertility.

Usage in Pregnancy: There are no adequate and well-controlled studies in pregnant women. Embryocidal effects were observed in rabbits. Therefore, captopril should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.

(Continued on adjacent page)

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ACE* INHIBITOR

Capoten®
(captopril tablets)
FOR HYPERTENSION†-PLUS

NEW–BID DOSAGE

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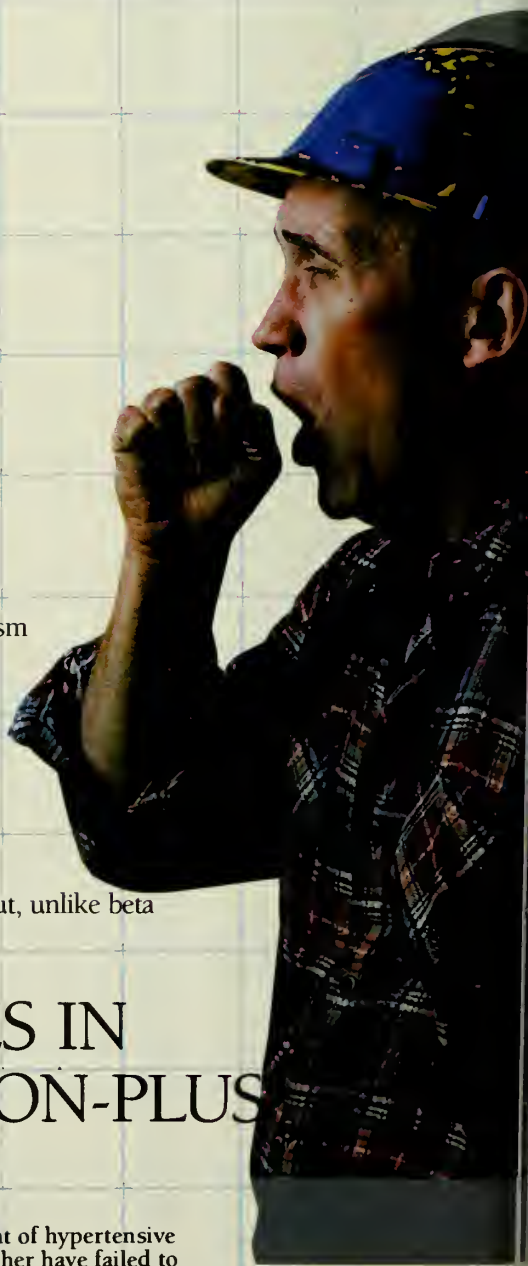
+ DIABETES† (14%)

CAPOTEN does not mask the warning symptoms of hypoglycemia, unlike some beta blockers

+ BRONCHOSPASTIC PULMONARY DISEASE† (7%)

CAPOTEN rarely causes bronchospasm



+ HEART FAILURE† (13%)

CAPOTEN improves cardiac output, unlike beta blockers

MORE PLUSES IN HYPERTENSION-PLUS

*Angiotensin Converting Enzyme

†CAPOTEN is indicated for the treatment of hypertensive patients who on multidrug regimens either have failed to respond satisfactorily or have developed unacceptable side effects.

Please see Precautionary Guidelines for use of CAPOTEN and brief summary of prescribing information accompanying this advertisement.

(Continued from Page 447)

EPITOMES—IMPORTANT ADVANCES IN CLINICAL MEDICINE

General Surgery

Items of progress in general surgery. Each item in the judgment of a panel of knowledgeable physicians has recently become reasonably firmly established, both as to scientific fact and important clinical significance.

537 **Arm Veins—Durable Autogenous Alternatives for Arterial Bypass**
GEORGE ANDROS, MD, and ROBERT W. HARRIS, MD

537 **Needle Aspiration of the Thyroid Gland**
MELVIN A. BLOCK, MD

538 **Use of Computed Tomography in Cases of Blunt Abdominal Trauma**
DONALD TRUNKEY, MD

539 **Liver Transplantation**
RICHARD E. WARD, MD, and E. STEVE WOODLE, MD

539 **Surgical Treatment of Morbid Obesity**
EDWARD A. DAINKO, MD

540 **Limb Salvage for Soft Tissue Sarcoma of the Extremities**
ARMANDO E. GIULIANO, MD, and FREDERICK R. EILBER, MD

540 **Ex Vivo Renal Artery Reconstruction**
RONALD J. STONEY, MD, and CRAIG KENT, MD

541 **Preoperative Biliary Tract Drainage**
HENRY A. PITT, MD

541 **Percutaneous Abscess Drainage and Related Radiologic Procedures**
ERIC vanSONNENBERG, MD

542 **Anal Sphincter-Saving Operations**
THOMAS R. RUSSELL, MD

543 **Splenic Salvage**
LEON MORGENSTERN, MD

543 **Conservative Surgical Treatment of Carcinoma of the Breast**
JOHN J. COYLE, MD

EDITORIALS

545 **Some Side Effects of Science and Technology on Medical Practice**

546 **Evaluation and Treatment of Impotence—Where Are We Going?**
TOM F. LUE, MD
Dr Lue is Assistant Professor, Department of Urology, University of California, San Francisco, School of Medicine.

546 **Food for Thought**

547 **Stress and Coping in Internal Medicine Residency**
MOLLY COOKE, MD
Dr Cooke is Assistant Clinical Professor, Department of Medicine, San Francisco General Hospital Medical Center, University of California, San Francisco, School of Medicine.

CASE REPORTS

549 **Rhabdomyolysis and Acute Renal Failure Following the Bite of the Giant Desert Centipede *Scolopendra heros***
JOY L. LOGAN, MD, and DAVID A. OGDEN, MD
From the Department of Internal Medicine, University of Arizona Health Sciences Center, Tucson.

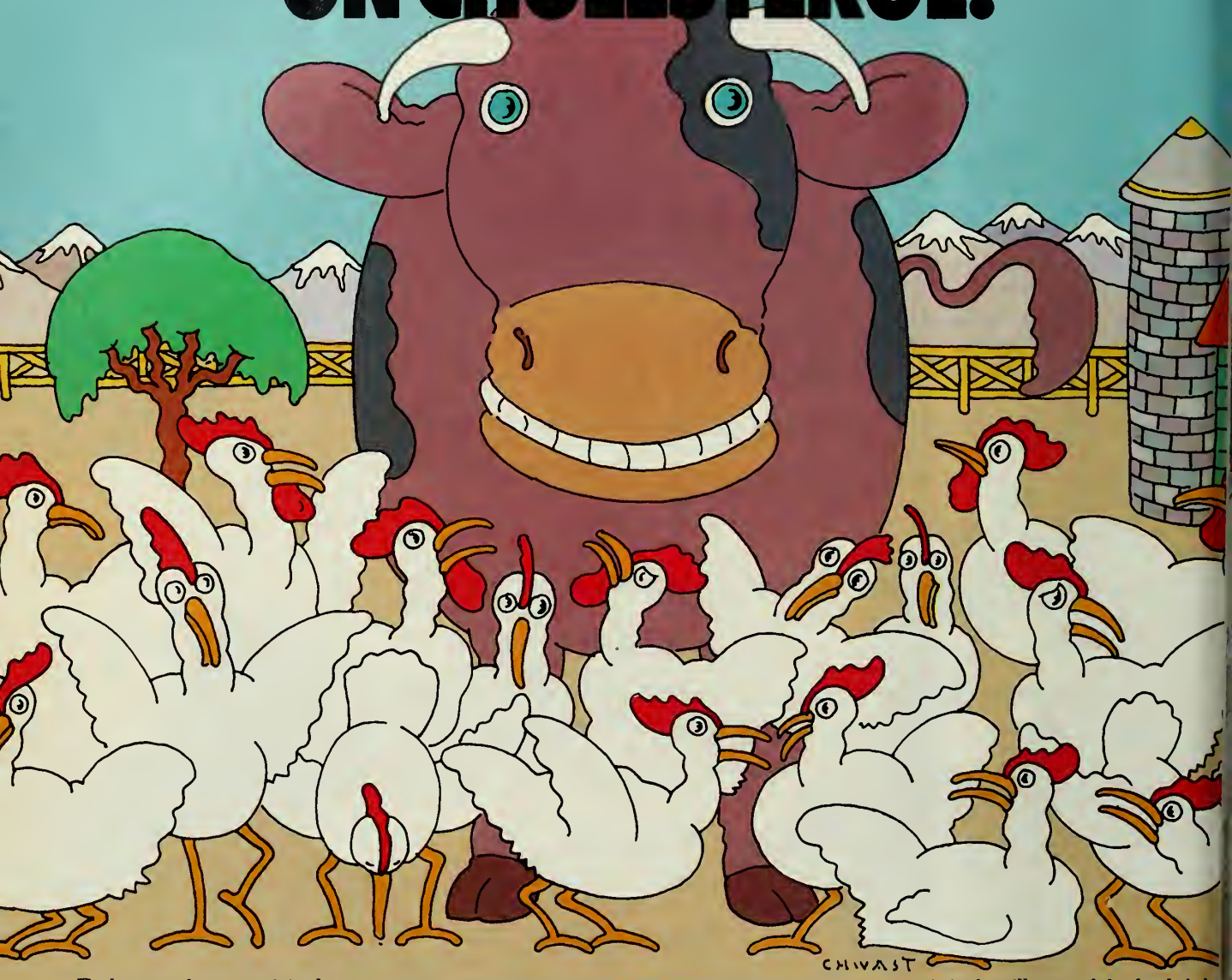
550 **A Case of Hyperthyroidism Presenting as Recurrent Pneumonia**
MARK J. ROSENTHAL, MD, and JAMES S. GOODWIN, MD
From the Department of Medicine, University of New Mexico School of Medicine, Albuquerque.

552 **ERCP Documentation of Pancreatic Ascites and Cystoenteric Fistula**
STEVEN BROZINSKY, MD
From the Division of Gastroenterology, Department of Medicine, University of California, San Diego, Medical Center, San Diego.

554 **Maggot Therapy Revisited**
JURIS BUNKIS, MD; SCOTT GHERINI, MD, and ROBERT L. WALTON, MD
From San Francisco General Hospital Medical Center and the Division of Plastic and Reconstructive Surgery, Department of Surgery, University of California, San Francisco, School of Medicine. Dr Walton is now Associate Professor and Chair, Plastic Surgery Division, Department of Surgery, University of Massachusetts Medical School, Worcester.

(Continued on Page 468)

ANNOUNCING SOME NEW FINDINGS ON CHOLESTEROL.



Perhaps rather surprisingly, beef has no more cholesterol than chicken. Even roast chicken without skin.

That was the finding of a new U.S.D.A. study on beef nutrient composition.*

That same study found beef is lower in calories than ever.

And lower in fat.

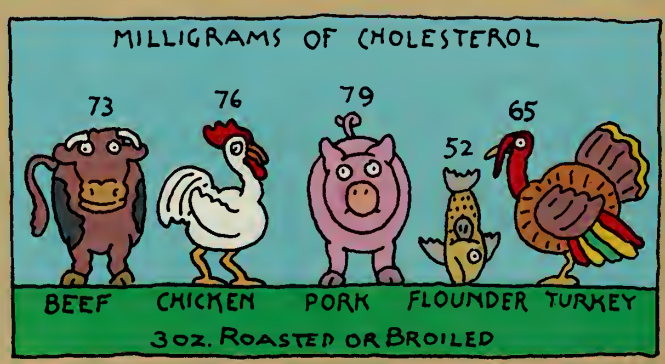
In fact, three ounces of beef now has just 192 calories and a modest nine grams of fat, over half of which is unsaturated.

Today, new breeding and feeding techniques are making beef a whole different animal. Though not so different that it isn't still one of the body's be sources of iron, zinc, B-vitami and protein.

It all means moderate portions of beef can fit easily ir a reduced cholesterol, low satu rated fat diet.

And that can stop a lot of squawking when you recom mend one.

For more information on the new U.S.D.A. study and beef's contribution to healthy eating in the eighties, write to Beef Nutrition, California Be Council, 551 Foster City Boulevard, Suite A, Foster City, California 94404.



*Beef data from 1983 Beef Nutritive Composition Studies conducted by the U.S.D.A. and National Live Stock and Meat Board.

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Continuing Medical Education

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CALIFORNIA, HAWAII AND NEVADA

This listing of continuing education programs in California, Hawaii and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Department of Continuing Medical Education, California Medical Association, 44 Gough St., San Francisco 94103; or phone (415) 863-5522. For a list of organizations approved for Category I credit toward the CMA Certificate in Continuing Medical Education or for more information on accreditation or certification, please write to the above address.

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 44 Gough Street, San Francisco 94103. (415) 863-5522.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Flora Harlee-Cordett, MS, MPH, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr., MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, ext. 2400.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 563-4321, ext. 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 497-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0328.

UCI: University of California, Irvine
Contact: E. R. Jennings, MD, Assistant Dean, University of California, Irvine, California College of Medicine, c/o UCI/CME Program, Memorial Hospital Medical Center, 2801 Atlantic Avenue, Long Beach 90801. (213) 595-3837, or (714) 856-5414, UCI Extension.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 452-3940.

UCSF: University of California, San Francisco
Contact: David S. Gullion, MD, Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 224-7051.

ALLERGY AND IMMUNOLOGY

April 18-20—**Allergy and Immunology for the Practicing Physician.** UCSF. Thursday-Saturday. 18 hrs. Fee: $200.

ANESTHESIOLOGY

May 5-11—**12th Hawaiian Seminar on Clinical Anesthesia.** California Society of Anesthesiology at Sheraton Kauai Hotel, HA. Sunday-Saturday. 20 hrs. Contact: Education Programs Division, Calif. Society of Anesthesiology, 100 S. Ellsworth Ave., San Mateo, CA. (415) 348-1407.

May 17-22—**Anesthesiology Review Course.** UCSD at Vacation Village, San Diego. Friday-Wednesday. 38 hrs.

CANCER

April 19—**Cancer Care.** Mt. Diablo Hospital Medical Center. Concord. Friday. 6 hrs. Fee: $100. Contact: Deborah Kolhede, Mt. Diablo Hospital and Medical Center, (415) 647-2359.

April 24—**Exploring the Future of Cancer Cures.** USC at Pasadena Hilton Hotel, Pasadena. Wednesday. Contact: Linda Richie-Walker (213) 224-7368.

CARDIOLOGY

April 20—**Cardiac Lecture Series: Advances in Research.** Heart Institute of the Desert at Annenberg Center, Rancho Mirage. Saturday. 2 hrs. Contact: Eisenhower Medical Center, 39000 Bob Hope Dr., Rancho Mirage 92270. (619) 568-2900.

April 26-28—**Coronary Artery Disease and Sudden Death: Primary and Secondary Prevention.** International Medical Education Corp. at Hyatt Union Square, San Francisco. Friday-Sunday. 13 hrs. Fee: $295. Contact: IMEC, 64 Inverness Dr. East, Englewood, CO 80112

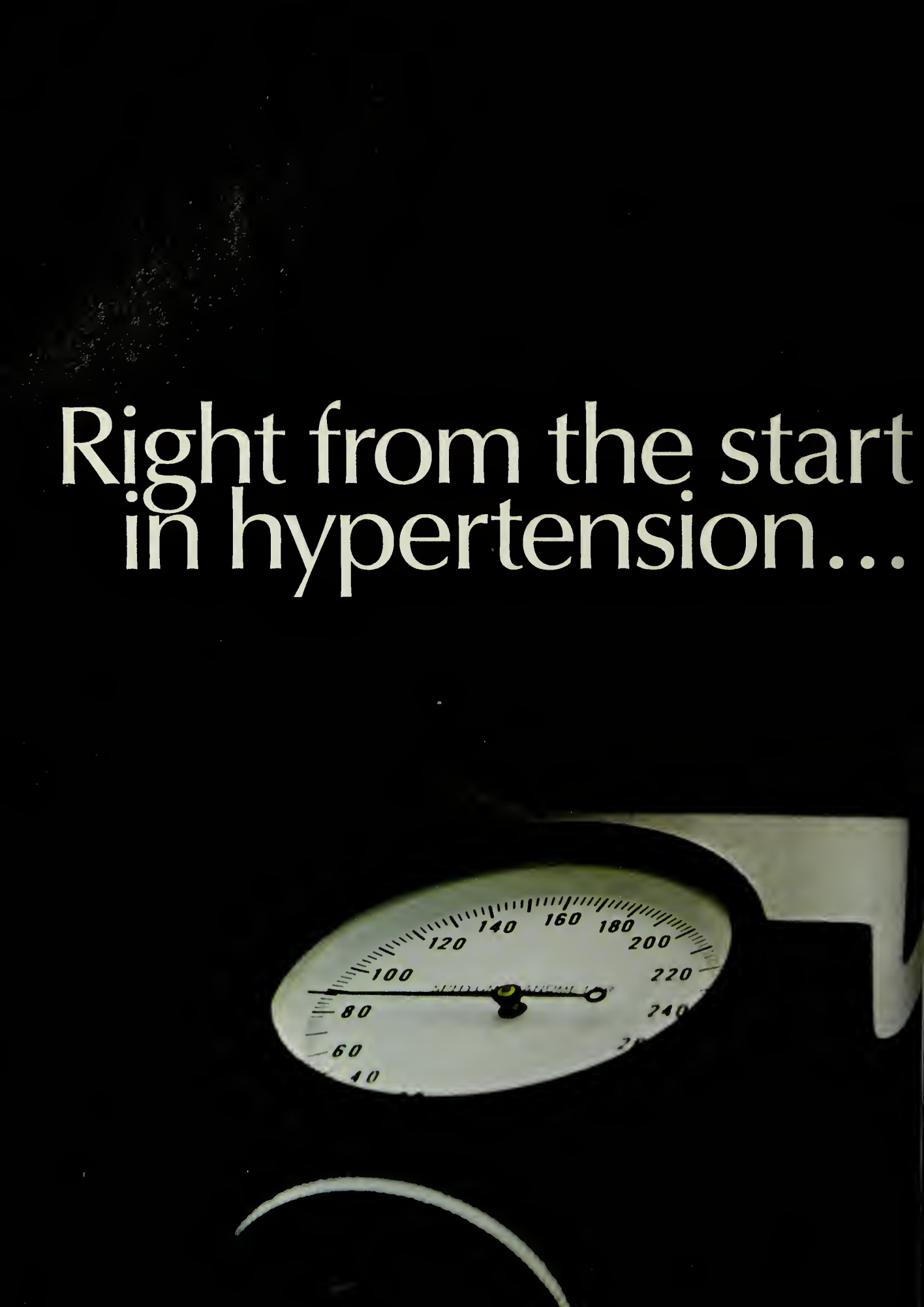
April 26-28—**Vascular and Pulmonary Disease: Diagnosis and Management.** Medical Education Resources at Renaissance Hotel, San Francisco. Friday-Sunday. 13 hrs. Fee: $275. Contact: Leslie Shaffer, Medical Education Res., 5808 S. Rapp St., Ste 202, Littleton, CO 80120. (303) 798-9862.

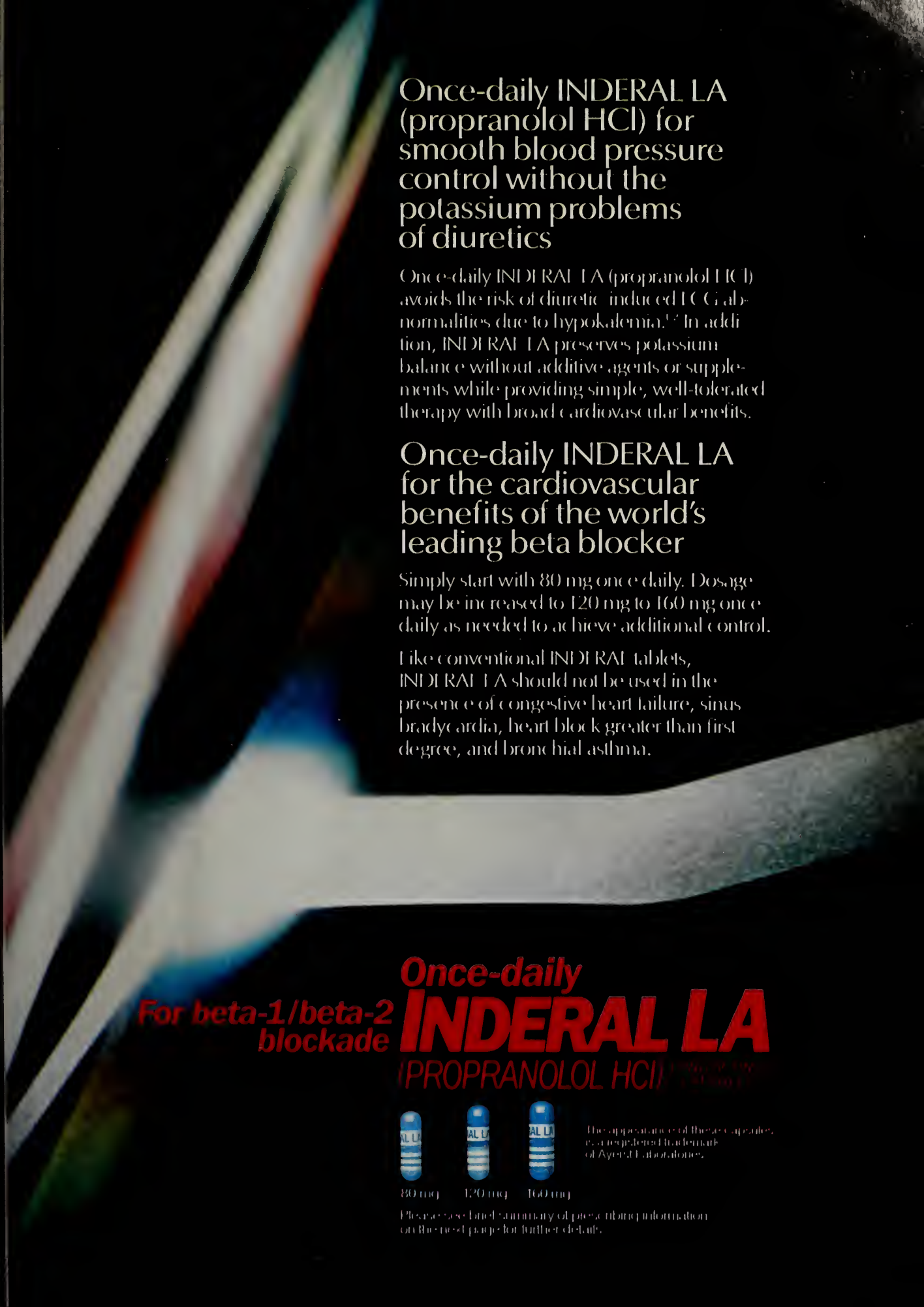
May 10-12—**Coronary Artery Disease and Sudden Death: Primary and Secondary Prevention.** International Medical Education Corp. at Hyatt Islandia, San Diego. Friday-Sunday. Contact: IMEC, Div. of Postgraduate & Continuing Medical Education, 64 Inverness Dr. E., Englewood, CO 80112.

June 16-20—**Western Thoracic Surgical Association Annual Meeting** at Hyatt Lake Tahoe, Incline Village. Sunday-Thursday. Contact: WTSA, 13 Elm Street, Manchester, MA 01944. (617) 927-8330.

(Continued on Page 457)

Right from the start in hypertension...





Once-daily INDERAL LA (propranolol HCl) for smooth blood pressure control without the potassium problems of diuretics

Once-daily INDERAL LA (propranolol HCl) avoids the risk of diuretic-induced ECG abnormalities due to hypokalemia.[1-7] In addition, INDERAL LA preserves potassium balance without additive agents or supplements while providing simple, well-tolerated therapy with broad cardiovascular benefits.

Once-daily INDERAL LA for the cardiovascular benefits of the world's leading beta blocker

Simply start with 80 mg once daily. Dosage may be increased to 120 mg to 160 mg once daily as needed to achieve additional control.

Like conventional INDERAL tablets, INDERAL LA should not be used in the presence of congestive heart failure, sinus bradycardia, heart block greater than first degree, and bronchial asthma.

For beta-1/beta-2 blockade

Once-daily

INDERAL LA

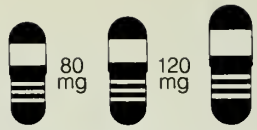
PROPRANOLOL HCl

80 mg 120 mg 160 mg

The appearance of these capsules is a registered trademark of Ayerst Laboratories.

Please see brief summary of prescribing information on the next page for further details.

Once-daily For beta-1/beta-2 blockade INDERAL® LA (PROPRANOLOL HCl) LONG ACTING CAPSULES



The appearance of these capsules is a registered trademark of Ayerst Laboratories

BRIEF SUMMARY *(FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE CIRCULAR.)*

INDERAL® LA brand of propranolol hydrochloride **(Long Acting Capsules)**

DESCRIPTION. Inderal LA is formulated to provide a sustained release of propranolol hydrochloride. Inderal LA is available as 80 mg, 120 mg, and 160 mg capsules.

CLINICAL PHARMACOLOGY. INDERAL is a nonselective beta-adrenergic receptor blocking agent possessing no other autonomic nervous system activity. It specifically competes with beta-adrenergic receptor stimulating agents for available receptor sites. When access to beta-receptor sites is blocked by INDERAL, the chronotropic, inotropic, and vasodilator responses to beta-adrenergic stimulation are decreased proportionately.

INDERAL LA Capsules (80, 120, and 160 mg) release propranolol HCl at a controlled and predictable rate. Peak blood levels following dosing with INDERAL LA occur at about 6 hours and the apparent plasma half-life is about 10 hours. When measured at steady state over a 24-hour period the areas under the propranolol plasma concentration-time curve (AUCs) for the capsules are approximately 60% to 65% of the AUCs for a comparable divided daily dose of INDERAL tablets. The lower AUCs for the capsules are due to greater hepatic metabolism of propranolol, resulting from the slower rate of absorption of propranolol. Over a twenty-four (24) hour period, blood levels are fairly constant for about twelve (12) hours then decline exponentially.

INDERAL LA should not be considered a simple mg for mg substitute for conventional propranolol and the blood levels achieved do not match (are lower than) those of two to four times daily dosing with the same dose. When changing to INDERAL LA from conventional propranolol, a possible need for retitration upwards should be considered especially to maintain effectiveness at the end of the dosing interval. In most clinical settings, however, such as hypertension or angina where there is little correlation between plasma levels and clinical effect, INDERAL LA has been therapeutically equivalent to the same mg dose of conventional INDERAL as assessed by 24-hour effects on blood pressure and on 24-hour exercise responses of heart rate, systolic pressure and rate pressure product. INDERAL LA can provide effective beta blockade for a 24-hour period.

The mechanism of the antihypertensive effect of INDERAL has not been established. Among the factors that may be involved in contributing to the antihypertensive action are (1) decreased cardiac output, (2) inhibition of renin release by the kidneys, and (3) diminution of tonic sympathetic nerve outflow from vasomotor centers in the brain. Although total peripheral resistance may increase initially, it readjusts to or below the pretreatment level with chronic use. Effects on plasma volume appear to be minor and somewhat variable. INDERAL has been shown to cause a small increase in serum potassium concentration when used in the treatment of hypertensive patients.

In angina pectoris, propranolol generally reduces the oxygen requirement of the heart at any given level of effort by blocking the catecholamine-induced increases in the heart rate, systolic blood pressure, and the velocity and extent of myocardial contraction. Propranolol may increase oxygen requirements by increasing left ventricular fiber length, end diastolic pressure and systolic ejection period. The net physiologic effect of beta-adrenergic blockade is usually advantageous and is manifested during exercise by delayed onset of pain and increased work capacity.

In dosages greater than required for beta blockade, INDERAL also exerts a quinidine-like or anesthetic-like membrane action which affects the cardiac action potential. The significance of the membrane action in the treatment of arrhythmias is uncertain.

The mechanism of the antimigraine effect of propranolol has not been established. Beta-adrenergic receptors have been demonstrated in the pial vessels of the brain.

Beta receptor blockade can be useful in conditions in which, because of pathologic or functional changes, sympathetic activity is detrimental to the patient. But there are also situations in which sympathetic stimulation is vital. For example, in patients with severely damaged hearts, adequate ventricular function is maintained by virtue of sympathetic drive which should be preserved. In the presence of AV block, greater than first degree, beta blockade may prevent the necessary facilitating effect of sympathetic activity on conduction. Beta blockade results in bronchial constriction by interfering with adrenergic bronchodilator activity which should be preserved in patients subject to bronchospasm.

Propranolol is not significantly dialyzable.

INDICATIONS AND USAGE. Hypertension: INDERAL LA is indicated in the management of hypertension; it may be used alone or used in combination with other antihypertensive agents, particularly a thiazide diuretic. INDERAL LA is not indicated in the management of hypertensive emergencies.

Angina Pectoris Due to Coronary Atherosclerosis: INDERAL LA is indicated for the long-term management of patients with angina pectoris.

Migraine: INDERAL LA is indicated for the prophylaxis of common migraine headache. The efficacy of propranolol in the treatment of a migraine attack that has started has not been established and propranolol is not indicated for such use.

Hypertrophic Subaortic Stenosis: INDERAL LA is useful in the management of hypertrophic subaortic stenosis, especially for treatment of exertional or other stress-induced angina, palpitations, and syncope. INDERAL LA also improves exercise performance. The effectiveness of propranolol hydrochloride in this disease appears to be due to a reduction of the elevated outflow pressure gradient which is exacerbated by beta-receptor stimulation. Clinical improvement may be temporary.

CONTRAINDICATIONS. INDERAL is contraindicated in 1) cardiogenic shock; 2) sinus bradycardia and greater than first degree block; 3) bronchial asthma, 4) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL.

WARNINGS. CARDIAC FAILURE: Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta blockade may precipitate more severe failure. Although beta blockers should be avoided in overt congestive heart failure, if necessary, they can be used with close follow-up in patients with a history of failure who are well compensated and are receiving digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle.

IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta blockers can, in some cases, lead to cardiac failure. Therefore, at the first sign or symptom of heart failure, the patient should be digitalized and/or treated with diuretics, and the response observed closely; or INDERAL should be discontinued (gradually, if possible).

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following abrupt discontinuance of INDERAL therapy. Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced over at least a few weeks, and the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)—PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

MAJOR SURGERY: The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

INDERAL (propranolol HCl), like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in starting and maintaining the heartbeat has also been reported with beta blockers.

DIABETES AND HYPOGLYCEMIA: Beta-adrenergic blockade may prevent the appearance of certain premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia in labile insulin-dependent diabetes. In these patients, it may be more difficult to adjust the dosage of insulin.

THYROTOXICOSIS: Beta blockade may mask certain clinical signs of hyperthyroidism. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

PRECAUTIONS. *General:* Propranolol should be used with caution in patients with impaired hepatic or renal function. INDERAL (propranolol HCl) is not indicated for the treatment of hypertensive emergencies.

Beta adrenoreceptor blockade can cause reduction of intraocular pressure. Patients should be told that INDERAL may interfere with the glaucoma screening test. Withdrawal may lead to a return of increased intraocular pressure.

Clinical Laboratory Tests: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

DRUG INTERACTIONS: Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if INDERAL is administered. The added catecholamine-blocking action may produce an excessive reduction of resting sympathetic nervous activity which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In 18-month studies in both rats and mice, employing doses up to 150 mg/kg/day, there was no evidence of significant drug-induced toxicity. There were no drug-related tumorigenic effects at any of the dosage levels. Reproductive studies in animals did not show any impairment of fertility that was attributable to the drug.

Pregnancy: Pregnancy Category C. INDERAL has been shown to be embryotoxic in animal studies at doses about 10 times greater than the maximum recommended human dose. There are no adequate and well-controlled studies in pregnant women. INDERAL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: INDERAL is excreted in human milk. Caution should be exercised when INDERAL is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS. Most adverse effects have been mild and transient and have rarely required the withdrawal of therapy.

Cardiovascular: bradycardia, congestive heart failure, intensification of AV block, hypotension, paresthesia of hands, thrombocytopenic purpura, arterial insufficiency, usually of the Raynaud type.

Central Nervous System: lightheadedness; mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia, visual disturbances, hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Gastrointestinal: nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis.

Allergic: pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Respiratory: bronchospasm.

Hematologic: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Auto-Immune: In extremely rare instances, systemic lupus erythematosus has been reported.

Miscellaneous: alopecia, LE-like reactions, psoriasiform rashes, dry eyes, male impotence, and Peyronie's disease have been reported rarely. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been associated with propranolol.

DOSAGE AND ADMINISTRATION. INDERAL LA provides propranolol hydrochloride in a sustained-release capsule for administration once daily. If patients are switched from INDERAL tablets to INDERAL LA capsules, care should be taken to assure that the desired therapeutic effect is maintained. INDERAL LA should not be considered a simple mg for mg substitute for INDERAL. INDERAL LA has different kinetics and produces lower blood levels. Retitration may be necessary especially to maintain effectiveness at the end of the 24-hour dosing interval.

HYPERTENSION—*Dosage must be individualized.* The usual initial dosage is 80 mg INDERAL LA once daily, whether used alone or added to a diuretic. The dosage may be increased to 120 mg once daily or higher until adequate blood pressure control is achieved. The usual maintenance dosage is 120 to 160 mg once daily. In some instances a dosage of 640 mg may be required. The time needed for full hypertensive response to a given dosage is variable and may range from a few days to several weeks.

ANGINA PECTORIS—*Dosage must be individualized.* Starting with 80 mg INDERAL LA once daily, dosage should be gradually increased at three to seven day intervals until optimum response is obtained. Although individual patients may respond at any dosage level, the average optimum dosage appears to be 160 mg once daily. In angina pectoris, the value and safety of dosage exceeding 320 mg per day have not been established.

If treatment is to be discontinued, reduce dosage gradually over a period of a few weeks (see WARNINGS).

MIGRAINE—*Dosage must be individualized.* The initial oral dose is 80 mg INDERAL LA once daily. The usual effective dose range is 160-240 mg once daily. The dosage may be increased gradually to achieve optimum migraine prophylaxis. If a satisfactory response is not obtained within four to six weeks after reaching the maximum dose, INDERAL LA therapy should be discontinued. It may be advisable to withdraw the drug gradually over a period of several weeks.

HYPERTROPHIC SUBAORTIC STENOSIS—80-160 mg INDERAL LA once daily.

PEDIATRIC DOSAGE—At this time the data on the use of the drug in this age group are too limited to permit adequate directions for use.

REFERENCES

1. Holland OB, Nixon JV, Kuhnert L: Diuretic-induced ventricular ectopic activity. *Am J Med* 1981;70:762-768. **2.** Holme I, Helgeland A, Hjermann I, et al: Treatment of mild hypertension with diuretics. The importance of ECG abnormalities in the Oslo study and in MRFIT. *JAMA* 1984;251:1298-1299.

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(Continued from Page 453)

June 21-23—**Diagnosis and Management of the Acute M.I.** International Medical Education Corp. at Hyatt Regency, Lake Tahoe. Friday-Sunday. 13 hrs. Fee: $295. Contact: IMEC, 64 Inverness Dr. E., Englewood, CO 80112.

June 25-27—**Vascular and Pulmonary Disease: Diagnosis and Management.** Medical Education Resources at Balboa Bay Club, Newport Beach. Tuesday-Thursday. 13 hrs. Fee: $275. Contact: Mrs Leslie Shaffer, Medical Education Resources, 5808 S. Rapp Street, Ste. 202, Littleton, CO 80120. (303) 798-9682.

June 26-28—**Consultative Cardiology: Update in Diagnostic and Therapeutic Techniques.** American College of Cardiology at Westin South Coast Plaza, Costa Mesa. Wednesday-Friday. Contact: American College of Cardiology, 9111 Old Georgetown Rd., Bethesda, MD 20814.

June 28-30—**ECG Interpretation and Arrhythmia Management.** International Medical Education Corp. at Disneyland Hotel, Anaheim. Friday-Sunday. 13 hrs. Fee: $295. Contact: IMEC, 64 Inverness Dr. E, Englewood, CO 80112.

EMERGENCY MEDICINE

April 24-26—**Clinical Advances and Research Updates in Emergency Medicine.** UCSF at Holiday Inn—Golden Gateway, San Francisco. Wednesday-Friday. 15 hrs. Fee: $300.

May 6-10—**Postgraduate Institute for Emergency Physicians, Symposium I.** UCSD at Vacation Village, San Diego. One Week. 13-16 hrs. Fee: $200-675.

May 10-11—**2nd Annual Emergency Symposium.** Kaiser Permanente, Los Angeles at Century Plaza Hotel, Century City. Friday-Saturday. 10.5 hrs. Fee: $150. Contact: Dept. of Clinical Services, Southern Kaiser Permanente Medical Group, 4747 Sunset Blvd., Los Angeles 90024. (213) 667-4241.

May 13-19—**Update in Trauma.** University of Arizona at California Wine Country. Monday-Sunday. 24 hrs. Contact: Richard Paris, MD, PO Box 209, Sun Valley, ID 83353. (208) 788-4995.

May 15-19—**Wound Management Workshop.** UCSD at Holiday Inn at the Embarcadero, San Diego. Monday-Friday. 19 hrs.

May 20-24—**Topics in Emergency Medicine.** UCSF at Sheraton at Fishermans Wharf, San Francisco. Monday-Friday. 33 hrs. Fee: $400.

June 20-21—**6th Annual Trauma Seminar.** Charles R. Drew Postgraduate Medical School at Disneyland Hotel, Anaheim. Thursday-Friday. 16 hrs. Contact: Dr. S. Bala, (213) 603-4510.

June 24-28—**Postgraduate Institute for Emerg. Physicians, Symposium 111.** UCSD at Hanalei Hotel, San Diego. Monday-Friday. 13-36 hrs. Fee: $200-675.

June 27-30—**Update in Emergency Medicine.** Mercy Medical Center, Redding at Salmon River (Whitewater rafting trip). Thursday-Sunday. 10 hrs. Fee: $125. Contact: Shelly Underwood, Mercy Medical Center, Redding, PO Box 6009, Redding, CA 96099-6009. (916) 243-2121.

INTERNAL MEDICINE

April 22-24—**Advances in Infectious Diseases.** UCSF at Mark Hopkins Hotel, San Francisco. Monday-Wednesday. Fee: $325.

April 24—**Thyroid '85.** The Hospital of the Good Samaritan at Hyatt Regency Hotel, Los Angeles. Wednesday. 6 hrs. Contact: Dolores Gay, 616 South Witmer St., Los Angeles 90017. (213) 977-2352.

April 27—**Nephrology.** UCSF at Fresno. Saturday.

May 8—**Gastroenterology: G.I. Bleeding.** LLU. Wednesday. 4 hrs.

May 13-17—**Advances in Internal Medicine.** UCSF. Wednesday-Sunday. Fee: $465.

May 17-18—**Clinical Concerns in Hemodialysis Therapy.** Rutgers Medical School at Sheraton Harbor Island West Hotel, San Diego. Friday-Saturday. 11.5 hrs. Contact: Richard A. Sherman, MD, Academic Health Science Center, UMDNJ-Rutgers Medical School, CN-19, New Brunswick, NJ 08903.

June 15-22—**7th Annual Liver Biopsy Workshop.** Liver Research and Educational Foundation and USC at Mauna Kea Beach Hotel, Hawaii. Saturday-Saturday. 28 hrs. Contact: Jerry McDaniel Travel Management, (213) 658-7777.

June 19-21—**Gastroenterology: Recent Developments in Theory and Practice.** UCSF at Mark Hopkins Hotel, San Francisco. Wednesday-Friday. Fees: $375.

June 21-23—**California Society of Internal Medicine—Annual Meeting** at Hotel Del Coronado, Coronado. Friday-Sunday. 3 hrs. Contact: Carol Holland Parlette, CSIM, 703 Market Street, San Francisco 94103.

June 24-28—**Advances in Internal Medicine.** UCSF at Hotel Meridien, San Francisco. Fee: $420.

OBSTETRICS AND GYNECOLOGY

April 20—**Infertility Update III.** Scripps Clinic and Research Foundation at La Jolla. Saturday. Contact: Scripps Clinic and Research Foundation, 10666 N. Torrey Pines Rd, La Jolla 92037. (619) 455-9100.

(Continued on Page 462)

The Western Journal of Medicine

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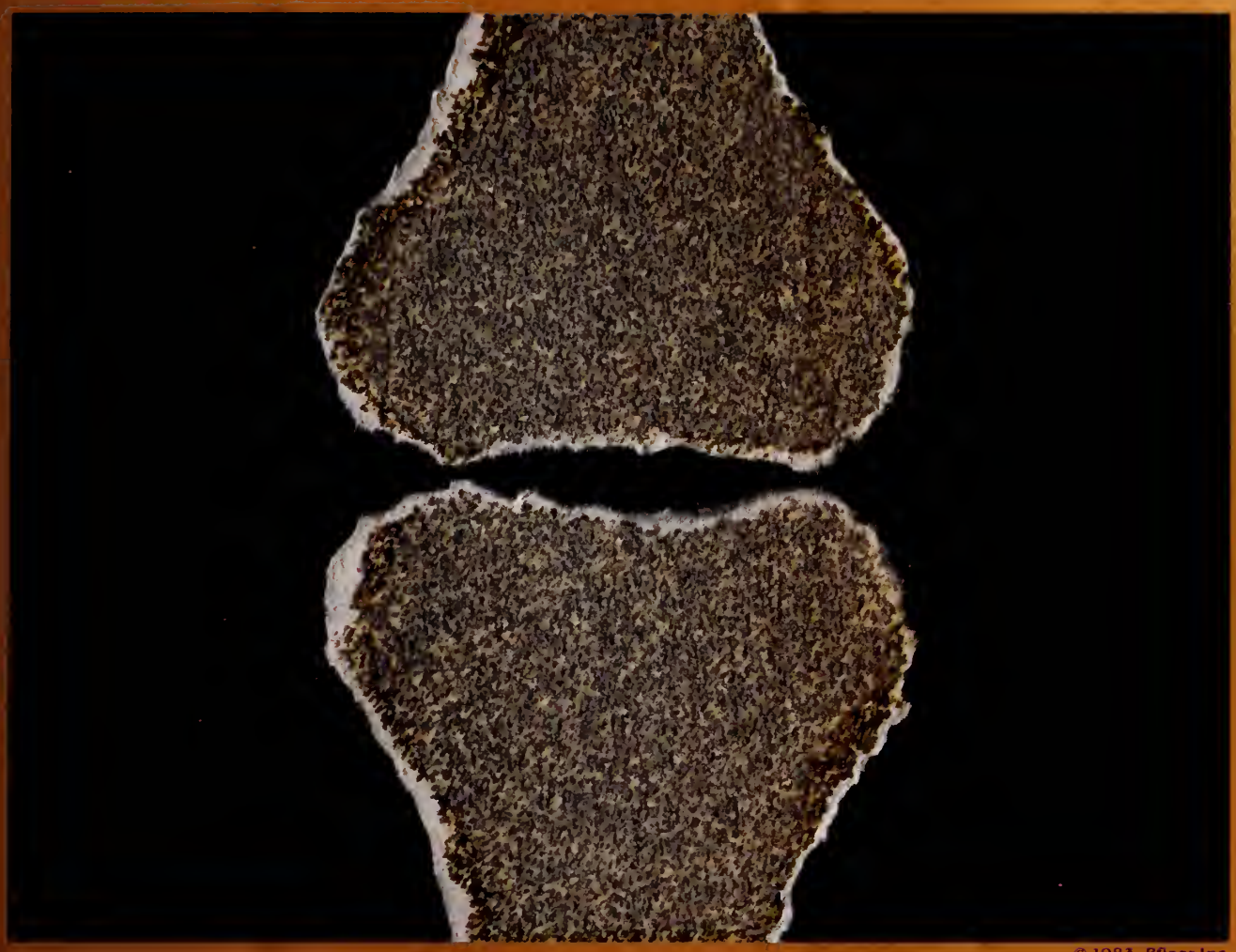

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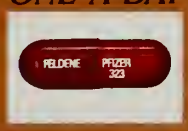

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Feldene®
(PIROXICAM) 20 mg capsules

20 mg once-a-day for initiation and maintenance

Prescribing Information

FELDENE® (piroxicam) Capsules *For Oral Use*

DESCRIPTION FELDENE (piroxicam) is 4-Hydroxy-2-methyl-*N*-2-pyridinyl-2*H*-1,2-benzothiazine-3-carboxamide 1,1-dioxide, an oxicam. Members of the oxicam family are not carboxylic acids, but they era acidic by virtue of the enolic 4-hydroxy substituent. FELDENE occurs as a white crystalline solid, speringly soluble in water, dilute acid and most organic solvents. It is slightly soluble in alcohols and in aqueous alkaline solution. It exhibits a weakly acidic 4-hydroxy proton (pKa 5.1) and a weakly basic pyridyl nitrogen (pKa 1.8).

CLINICAL PHARMACOLOGY FELDENE has shown anti-inflammatory, analgasic and antipyretic properties in animals. Edema, erythema, tissue proliferation, fever, and pain can all be inhibited in laboratory animals by the administration of FELDENE. It is effective regardless of the etiology of the inflammation. The mode of action of FELDENE is not fully established at this time. However, a common mechanism for the above effects may exist in the ability of FELDENE to inhibit the biosynthesis of prostaglandins, known mediators of inflammation.

It is established that FELDENE does not act by stimulating the pituitary-adrenal axis.

FELDENE is well absorbed following oral administration. Drug plasma concentrations are proportional for 10 and 20 mg doses, generally peak within three to five hours after medication, and subsequently decline with a mean half-life of 50 hours (range of 30 to 86 hours, although values outside of this range have been encountered).

This prolonged half-life results in the maintenance of relatively stable plasma concentrations throughout the day on once daily doses and to significant drug accumulation upon multiple dosing. A single 20 mg dose generally produces peak piroxicam plasma levels of 1.5 to 2 mcg/ml, while maximum drug plasma concentrations, after repeated daily ingestion of 20 mg FELDENE, usually stabilize at 3-8 mcg/ml. Most patients approximate steady state plasma levels within 7 to 12 days. Higher levels, which approximate steady state at two to three weeks, have been observed in patients in whom longer plasma half-lives of piroxicam occurred.

FELDENE and its biotransformation products are excreted in urine and feces, with about twice as much appearing in the urine as the feces. Metabolism occurs by hydroxylation at the 5 position of the pyridyl side chain and conjugation of this product; by cyclodehydration, and by a sequence of reactions involving hydrolysis of the amide linkage, decarboxylation, ring contraction, and N-demethylation. Less than 5% of the daily dose is excreted unchanged.

Concurrent administration of aspirin (3900 mg/day) and FELDENE (20 mg/day), resulted in a reduction of plasma levels of piroxicam to about 80% of their normal values. The use of FELDENE in conjunction with aspirin is not recommended because data are inadequate to demonstrate that the combination produces greater improvement than that achieved with aspirin alone and the potential for adverse reactions is increased. Concomitant administration of antacids had no effect on FELDENE plasma levels. The effects of impaired renal function or hepatic disease on plasma levels have not been established.

FELDENE, like salicylates and other nonsteroidal anti-inflammatory agents, is associated with symptoms of gastrointestinal tract irritation (see ADVERSE REACTIONS). However, in a study utilizing ^{51}Cr-tagged red blood cells, 20 mg of FELDENE administered as a single dose for four days did not result in a significant increase in fecal blood loss and did not detectably affect the gastric mucosa. In the same study a total daily dose of 3900 mg of aspirin, i.e., 972 mg q.i.d. caused a significant increase in fecal blood loss and mucosal lesions as demonstrated by gastroscopy.

In controlled clinical trials, the effectiveness of FELDENE has been established for both acute exacerbations and long-term management of rheumatoid arthritis and osteoarthritis.

The therapeutic effects of FELDENE are evident early in the treatment of both diseases with a progressive increase in response over several (8-12) weeks. Efficacy is seen in terms of pain relief and, when present, subsidence of inflammation.

Doses of 20 mg/day FELDENE display a therapeutic effect comparable to therapeutic doses of aspirin, with a lower incidence of minor gastrointestinal effects and tinnitus.

FELDENE has been administered concomitantly with fixed doses of gold and corticosteroids. The existence of a "steroid-sparing" effect has not been adequately studied to date.

INDICATIONS AND USAGE FELDENE is indicated for acute or long-term use in the relief of signs and symptoms of the following:

1. osteoarthritis
2. rheumatoid arthritis

Dosage recommendations for use in children have not been established.

CONTRAINDICATIONS FELDENE should not be used in patients who have previously exhibited hypersensitivity to it, or in individuals with the syndrome comprised of bronchospasm, nasal polyps, and angioedema precipitated by aspirin or other nonsteroidal anti-inflammatory drugs.

WARNINGS Peptic ulceration, perforation, and G.I. bleeding—sometimes severe, and, in some instances fatal—have been reported with patients receiving FELDENE. If FELDENE must be given to patients with a history of upper gastrointestinal tract disease, the patient should be under close supervision (see ADVERSE REACTIONS). In controlled clinical trials, incidence of peptic ulceration with the maximum recommended FELDENE capsule dose of 20 mg per day was 0.8%. The use of dosas higher than the recommended dose is associated with an increase in the incidence of gastrointestinal irritation and ulcers.

PRECAUTIONS As with other anti-inflammatory agents, long-term administration to animals results in renal papillary necrosis and related pathology in rats, mice, and dogs.

Acute renal failure and hyperkalemia as well as reversible elevations of BUN and serum creatinine have been raported with FELDENE. The effect is thought to result from inhibition of renal prostaglandin synthesis resulting in a change in medullary and deep cortical blood flow with an attendant effect on renal function. Patients with impaired renal function and on diuretics as well as elderly patients who have decreased renal function are more at risk. Because of the extensive renal excretion of piroxicam and its biotransformation products (less than 5% of the daily dose excreted unchanged, see CLINICAL PHARMACOLOGY), lower doses of piroxicam should be anticipated in patients with impaired renal function and they should be carefully monitored. In addition to reversible changes in renal function, interstitial nephritis, glomerulitis, papillary necrosis and the nephrotic syndrome have been reported with FELDENE.

Although other nonsteroidal anti-inflammatory drugs do not have the same direct effects on platelets that aspirin does, all drugs inhibiting prostaglendin biosynthesis do interfere with platelet function to some degree; therefore, patients who may be adversely affected by such an action should be carefully observed when FELDENE is administered.

Because of reports of adverse eye findings with nonsteroidal anti-inflammatory agents, it is recommended that patients who develop visual complaints during treatment with FELDENE have ophthalmic evaluation.

As with other nonsteroidal anti-inflammatory drugs, borderline elevations of one or more liver tests may occur in up to 15% of patients. These abnormalities may progress, may remain essentially unchanged, or may be transient with continued therapy. The SGPT (ALT) test is probably the most sensitive indicator of liver dysfunction. Meaningful (3 times the upper limit of normal) elevations of SGPT or SGOT (AST) occurred in controlled clinical trials in less than 1% of patients. A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of more severe hepatic reaction while on therapy with FELDENE. Severe hepatic reactions, including jaundice and cases of fatal hepatitis, have been reported with FELDENE. Although such reactions are rare, if abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g. eosinophilia, rash, etc.), FELDENE should be discontinued. (See also ADVERSE REACTIONS.)

Although at the recommended dose of 20 mg/day of FELDENE increased fecal blood loss due to gastrointestinal irritation did not occur (see CLINICAL PHARMACOLOGY), in about 4% of the patients treated with FELDENE alone or concomitantly with aspirin, reductions in hemoglobin and hematocrit values were observed. Therefore, these values should be determined if signs or symptoms of anemia occur.

Peripheral edema has been observed in approximately 2% of the patients treated with FELDENE. Therefore, as with other nonsteroidal anti-inflammatory drugs, FELDENE should be used with caution in patients with heart failure, hypertension or other conditions predisposing to fluid retention, since its usage may be associated with a worsening of these conditions.

A combination of dermatological and/or allergic signs and symptoms suggestive of serum sickness have occasionally occurred in conjunction with the use of FELDENE. These include arthralgias, pruritus, fever, fatigue, and rash including vesiculo bullous reactions and exfoliative dermatitis.

DRUG INTERACTIONS FELDENE is highly protein bound, and, therefore, might be expected to displace other protein-bound drugs. Although this has not occurred in *in vitro* studies with coumarin-type anticoagulants, interactions with coumerin-type anticoagulants have been reported with FELDENE since marketing; therefore, physicians should closely monitor patients for a change in dosage requirements when administering FELDENE (piroxicam) to patients on coumarin-type enticoagulants and other highly protein-bound drugs.

Plasma levels of piroxicam are depressed to approximately 80% of their normal values when FELDENE (piroxicam) is administered in conjunction with aspirin (3900 mg/day), but concomitant administration of antacids has no effect on piroxicam plasma levels (see CLINICAL PHARMACOLOGY).

Nonsteroidal anti-inflammatory agents, including FELDENE, have been reported to increase steady state plasma lithium levels. It is recommended that plasma lithium levels be monitored when initiating, adjusting and discontinuing FELDENE.

Carcinogenesis, Chronic Animal Toxicity and Impairment of Fertility Subacute and chronic toxicity studies have been carried out in rats, mice, dogs, and monkeys.

The pathology most often seen was that characteristically associated with the animal toxicology of anti-inflammatory agents: renal papillary necrosis (see PRECAUTIONS) and gastrointestinal lesions.

In classical studies in laboratory animals piroxicam did not show any teratogenic potential.

Raproductive studies revaaled no impairment of fartility in animals.

Pregnancy and Nursing Mothers Like other drugs which inhibit the synthesis and release of prostaglandins, piroxicam increased the incidence of dystocia and delayed partunfion in pregnant animals when piroxicam administration was continued late into pregnancy. Gastrointestinel tract toxicity was increased in pregnant females in the last trimester of pregnancy compared to nonpregnant females or females in earlier trimestars of pregnancy.

FELDENE is not recommended for use in nursing mothers or in pragnant women because of the animal findings and since safety for such use has not been established in humans.

Use in Children Dosage recommendations and indications for usa in children have not been established.

ADVERSE REACTIONS The incidance of adverse reactions to piroxicam is based on clinical trials involving approximately 2300 patients, about 400 of whom were treated for more than one year and 170 for more than two years. About 30% of all patients receiving daily doses of 20 mg of FELDENE experienced side effects. Gastrointestinal symptoms were the most prominent side effects—occurring in approximately 20% of tha patients, which in most instances did not interfere with the course of therapy. Of the patients experiencing gastrointestinal side affects, approximately 5% discontinued therapy with an overall incidence of paptic ulceration of about 1%.

Other than the gastrointestinal symptoms, edema, dizziness, headache, changes in hematological parameters, and rash have been reportad in a small percentage of patients. Routine ophthalmoscopy and slit-lamp examinations have revealed no evidence of ocular changes in 205 patients followed from 3 to 24 months while on therapy.

Incidence Greater Than 1% The following adverse reactions occurred more frequently than 1 in 100.

Gastrointestinel: stomatitis, anorexia, epigastric distress*, nausea*, constipation, abdominal discomfort, flatulence, diarrhea, abdominal pain, indigestion

Hematological: decreases in hemoglobin* and hematocrit* (see PRECAUTIONS), anemia, leucopenia, eosinophilia

Dermatologic: pruritus, rash

Central Nervous System: dizziness, somnolence, vertigo

Urogenital: BUN and creatinine elavations (see PRECAUTIONS)

Body as a Whole: headache, malaise

Special Senses: tinnitus

Cardiovascular/Respiratory: edema (sae PRECAUTIONS)

*Reactions occurring in 3% to 9% of patients treated with FELDENE. Reactions occurring in 1-3% of patients are unmarked.

Incidence Less Than 1% (Causal Relationship Probable)

The following adverse reactions occurred less frequently than 1 in 100. The probability exists that there is a causal relationship between FELDENE and these reactions.

Gastrointestinal: liver function abnormalities, jaundice, hepatitis (see PRECAUTIONS), vomiting, hematemesis, melena, gastrointestinal bleeding, perforation and ulceration (see WARNINGS), dry mouth

Hematological: thrombocytopenia, petechial rash, ecchymosis, bona marrow depression including aplastic anemia, epistaxis

Dermatologic: sweating, erythema, bruising, desquamation, exfoliative dermatitis, arythema multiforme, toxic epidermal necrolysis, Stevens-Johnson syndrome, vesiculo bullous raaction, photoallergic skin reactions

Central Nervous System: depression, insomnia, nervousness

Urogenital: hematuria, proteinuria, interstitial nephritis, renal failure, hyperkalemia, glomerulitis, papillary necrosis, nephrotic syndrome (see PRECAUTIONS)

Body as a Whole. pain (colic), fever, flu-like syndrome (see PRECAUTIONS)

Special Senses: swollen eyes, blurred vision, eye irritations

Cardiovascular/Raspiratory: hypertension, worsening of congestive heart failure (see PRECAUTIONS), exacerbation of angina

Metabolic: hypoglycemia, hypergtycemia, weight increase, weight decrease

Hypersensitivity: anaphylaxis, bronchospasm, urticaria angioedeme, vesculitis, "serum sickness" (see PRECAUTIONS)

Incidence Less Than 1% (Ceusal Relationship Unknown)

Other advarse reactions were reported with a frequency of less than 1 in 100, but a causal relationship between FELDENE and the reaction could not be determined.

Gastrointestinal: pancraatitis

Dermatologic: onycholysis, loss of hair

Central Nervous System: akathisia, hallucinations, mood altarations, dream abnormalities, mental confusion, paresthesias

Urogenital System: dysuria

Body as a Whole. weakness

Cardiovascular/Respiratory: palpitations, dyspnea

Hypersensitivity: positive ANA

OVERDOSAGE: In the event treatment for overdosage is required the long plasma half-life (see CLINICAL PHARMACOLOGY) of piroxicam should be considered. The absence of experience with acute ovardosage precludes characterization of sequelae and recommendation of specific antidotal efficacy at this time. It is reasonable to assume, however, that the standard measures of gastric evacuation and general supportive therapy would apply. In addition to supportive measuras, the use of activated charcoal may effectively reduce the absorption and reabsorption of piroxicam. Experimants in dogs have demonstrated that the use of multiple-dose treatments with activated charcoal could reduce the half-life of piroxicam elimination from 27 hours (without charcoal) to 11 hours and reduce the systemic bioavailability of piroxicam by as much as 37% when activeted charcoal is given as late as 6 hours after administration of piroxicam.

ADMINISTRATION AND DOSAGE Rheumatoid Arthritis, Osteoarthritis It is recommended that FELDENE therapy be initiated and maintained at a single daily dose of 20 mg. If desired the daily dose may be divided. Because of the long half-life of FELDENE, steady-state blood levels are not reached for 7-12 days. Therefore although the therapeutic effects of FELDENE are evide early in treatment, there is a progressive increase in response over several weeks and the effect of therapy should not be assessed for two weeks.

Dosage recommendations and indications for use in children have not been established.

HOW SUPPLIED FELDENE Capsules for oral administration

Bottles of 100: 10 mg (NDC 0663-3220-66) maroon and blue #322
20 mg (NDC 0663-3230-66) meroon #323

Bottles of 500: 20 mg (NDC 0663-3230-73) maroon #323

Unit dose packages of 100: 20 mg (NDC 0663-3230-41) maroon #323

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Among leading benzodiazepines, only Ativan has proof... pharmacokinetics not significantly altered by age.[1]

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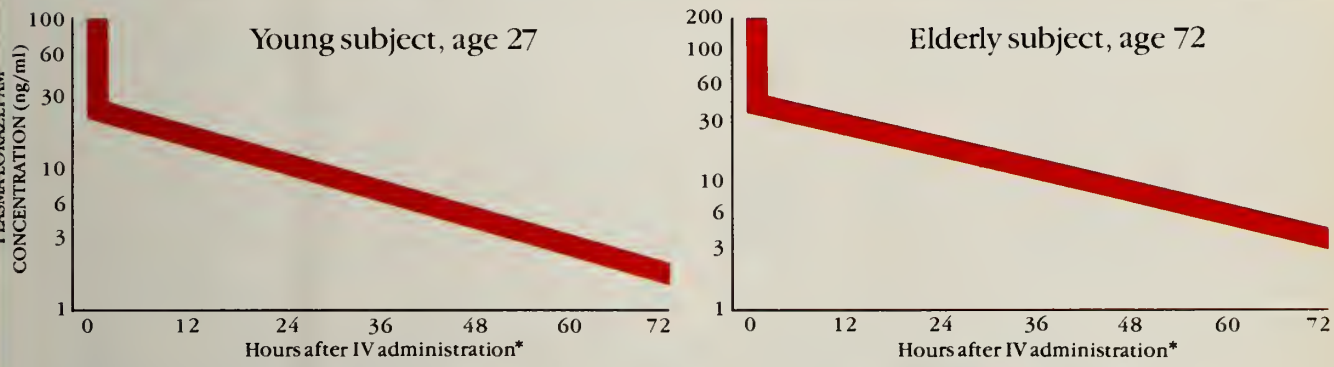

Lorazepam is nearly 100 percent bioavailable by the intramuscular and oral routes, as compared to the intravenous. Therefore, data for clearance of intravenous lorazepam are equally applicable to oral lorazepam.

- **Clearance not significantly delayed by age, liver or kidney dysfunction**
- **Cumulative sedative effects seldom a problem**
- **Available in 0.5-mg tablets to facilitate the recommended geriatric starting dosage**

1. Greenblatt DJ: Clinical study, pharmacokinetics and bioavailability in the elderly, Ativan® (lorazepam). Data on file, Wyeth Laboratories.

*Fourteen subjects, aged 60 to 84 years, participated in the study. Twelve subjects, aged 19 to 32 years, served as "young controls." Subject dosage was adjusted for body weight and ranged from 1.5 mg to 3.0 mg of lorazepam. Within the study, lorazepam clearance was monitored following IV, IM and oral administration in the elderly group and following IV administration in the control group. The effect of aging on total clearance of lorazepam was relatively small and not statistically significant. Half-life values following the three different routes of administration were essentially identical.

Only Ativan® (lorazepam) IV

Wyeth Laboratories
Philadelphia, PA 19101

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See important information on following page.

The appearance of these tablets is a registered trademark of Wyeth Laboratories

DISTINCTIVE DESIGN 0.5, 1.0 and 2.0 mg

Brief Summary of Prescribing Information.

Indications and Usage: Management of anxiety disorders or short-term relief of symptoms of anxiety or anxiety associated with depressive symptoms. Anxiety or tension associated with stress of everyday life usually does not require treatment with an anxiolytic.

Effectiveness in long-term use, i.e., more than 4 months, has not been assessed by systematic clinical studies. Reassess periodically usefulness of the drug for the individual patient.

Contraindications: Known sensitivity to benzodiazepines or acute narrow-angle glaucoma.

Warnings: Not recommended in primary depressive disorders or psychoses. As with all CNS-acting drugs, warn patients not to operate machinery or motor vehicles, and of diminished tolerance for alcohol and other CNS depressants.

Physical and Psychological Dependence: Withdrawal symptoms like those noted with barbiturates and alcohol have occurred following abrupt discontinuance of benzodiazepines (including convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Addiction-prone individuals, e.g. drug addicts and alcoholics, should be under careful surveillance when on benzodiazepines because of their predisposition to habituation and dependence. Withdrawal symptoms have also been reported following abrupt discontinuance of benzodiazepines taken continuously at therapeutic levels for several months.

Precautions: In depression accompanying anxiety, consider possibility for suicide.

For elderly or debilitated patients, initial daily dosage should not exceed 2mg to avoid oversedation. Terminate dosage gradually since abrupt withdrawal of any antianxiety agent may result in symptoms like those being treated: anxiety, agitation, irritability, tension, insomnia and occasional convulsions. Observe usual precautions with impaired renal or hepatic function. Where gastrointestinal or cardiovascular disorders coexist with anxiety, note that lorazepam has not been shown of significant benefit in treating gastrointestinal or cardiovascular component. Esophageal dilation occurred in rats treated with lorazepam for more than 1 year at 6mg/kg/day. No effect dose was 1.25mg/kg/day (about 6 times maximum human therapeutic dose of 10mg/day). Effect was reversible only when treatment was withdrawn within 2 months of first observation. Clinical significance is unknown; but use of lorazepam for prolonged periods and in geriatrics requires caution and frequent monitoring for symptoms of upper G.I. disease. Safety and effectiveness in children under 12 years have not been established.

ESSENTIAL LABORATORY TESTS: Some patients have developed leukopenia; some have had elevations of LDH. As with other benzodiazepines, periodic blood counts and liver function tests are recommended during long-term therapy.

CLINICALLY SIGNIFICANT DRUG INTERACTIONS: Benzodiazepines produce CNS depressant effects when administered with such medications as barbiturates or alcohol.

CARCINOGENESIS AND MUTAGENESIS: No evidence of carcinogenic potential emerged in rats during an 18-month study. No studies regarding mutagenesis have been performed.

PREGNANCY: Reproductive studies were performed in mice, rats, and 2 strains of rabbits. Occasional anomalies (reduction of tarsals, tibia, metatarsals, malrotated limbs, gastroschisis, malformed skull and microphthalmia) were seen in drug-treated rabbits without relationship to dosage. Although all these anomalies were not present in the concurrent control group, they have been reported to occur randomly in historical controls. At 40mg/kg and higher, there was evidence of fetal resorption and increased fetal loss in rabbits which was not seen at lower doses. Clinical significance of these findings is not known. However, increased risk of congenital malformations associated with use of minor tranquilizers (chlordiazepoxide, diazepam and meprobamate) during first trimester of pregnancy has been suggested in several studies. Because use of these drugs is rarely a matter of urgency, use of lorazepam during this period should almost always be avoided. Possibility that a woman of child-bearing potential may be pregnant at institution of therapy should be considered. Advise patients if they become pregnant to communicate with their physician about desirability of discontinuing the drug. In humans, blood levels from umbilical cord blood indicate placental transfer of lorazepam and its glucuronide.

NURSING MOTHERS: It is not known if oral lorazepam is excreted in human milk like other benzodiazepines. As a general rule, nursing should not be undertaken while on a drug since many drugs are excreted in milk.

Adverse Reactions, if they occur, are usually observed at beginning of therapy and generally disappear on continued medication or on decreasing dose. In a sample of about 3,500 anxious patients, most frequent adverse reaction is sedation (15.9%), followed by dizziness (6.9%), weakness (4.2%) and unsteadiness (3.4%). Less frequent are disorientation, depression, nausea, change in appetite, headache, sleep disturbance, agitation, dermatological symptoms, eye function disturbance, various gastrointestinal symptoms and autonomic manifestations. Incidence of sedation and unsteadiness increased with age. Small decreases in blood pressure have been noted but are not clinically significant, probably being related to relief of anxiety.

Transient amnesia or memory impairment has been reported in association with the use of benzodiazepines.

Overdosage: In management of overdosage with any drug, bear in mind multiple agents may have been taken. Manifestations of overdosage include somnolence, confusion and coma. Induce vomiting and/or undertake gastric lavage followed by general supportive care, monitoring vital signs and close observation. Hypotension, though unlikely, usually may be controlled with Levarterenol Bitartrate Injection U.S.P. Usefulness of dialysis has not been determined.

Ativan® (IV) **for** (lorazepam) **Anxiety**

DOSAGE: Individualize for maximum beneficial effects. Increase dose gradually when needed, giving higher evening dose before increasing daytime doses. Anxiety, usually 2-3mg/day given b.i.d. or t.i.d.; dosage may vary from 1 to 10mg/day in divided doses. For elderly or debilitated, initially 1-2mg/day; insomnia due to anxiety or transient situational stress, 2-4mg h.s.

HOW SUPPLIED: 0.5, 1.0 and 2.0mg tablets.

Wyeth Laboratories
Philadelphia, PA 19101

CONTINUING MEDICAL EDUCATION

(Continued from Page 457)

OPHTHALMOLOGY

May 18—**Neodymium—YAG Laser Course.** Jules Stein Eye Institute at Los Angeles. Saturday. 8 hrs. Fee: $200. Contact: Lu Hendricks, JSEI, 800 Westwood Plaza, Los Angeles 90024. (213) 825-4617.

June 6-8—**Cosmetic Blepharoplasty Workshop.** Jules Stein Eye Institute at Los Angeles. Thursday-Saturday. 18 hrs. Fee: $750. Contact: Lu Hendricks, JSEI, 800 Westwood Plaza, Los Angeles 90024. (213) 825-4617.

June 29-July 3—**Pacific Coast Oto-Ophthalmological Society Annual Meeting** at Hotel Del Coronado, Coronado. Saturday-Wednesday. Contact: Robert Christensen, MD, UCLA Med Center, 800 Westwood Plaza, Los Angeles, CA 90024.

PATHOLOGY

May 23-24—**Symposium on Current Issues in Anatomic Pathology.** UCSF. Thursday-Friday.

PEDIATRICS

April 17-19—**10th Annual Symposium "Care of the Sick Newborn."** UCI at Hyatt Regency Hotel, Long Beach. Wednesday-Friday. 17 hrs.

April 19-20—**Annual Pediatric Program.** UCD at Sacramento Inn, Sacramento. Friday-Sunday.

April 19-21—**3rd Annual Avoiding the Pitfalls of Pediatric Office Orthopedics.** UCLA at Americana Canyon Hotel, Palm Springs. Friday-Sunday. 10.5 hrs. Fee: $240.

May 13-17—**The 15th Annual Review of Pediatrics.** USC at Los Angeles. Monday-Friday. 26 hrs. Fee: $360.

May 15—**Los Angeles Pediatric Society—Annual Spring Meeting** at Los Angeles. Wednesday. Contact: Eve Black, Exec. Sec., PO Box 2022, Inglewood 90305. (213) 757-1198.

May 25-27—**Annual Spring Meeting, N. Calif. Chapter, American Academy of Pediatrics.** American Academy of Pediatrics at Hyatt Regency, Monterey. Saturday-Monday. 11 hrs. Contact: Am. Academy of Ped., (415) 459-4775. Fee: $125-$225.

May 30-June 1—**Pediatric Rehabilitation Program.** UCD at Doubletree Inn, Monterey. Thursday-Saturday.

June 21-22—**Pediatric Pulmonary Update—1985.** Children's Hospital and Health Center at San Diego Hilton Beach and Tennis Resort. Friday-Saturday. Contact: Sung Min Park, MD, Children's Hospital and Health Center, 8001 Frost Street, San Diego 92123. (619) 576-5854.

June 22-29—**3rd National Kaiser Permanente Pediatrics Conference** at Maui, Hawaii. One Week.

(Continued on Page 466)

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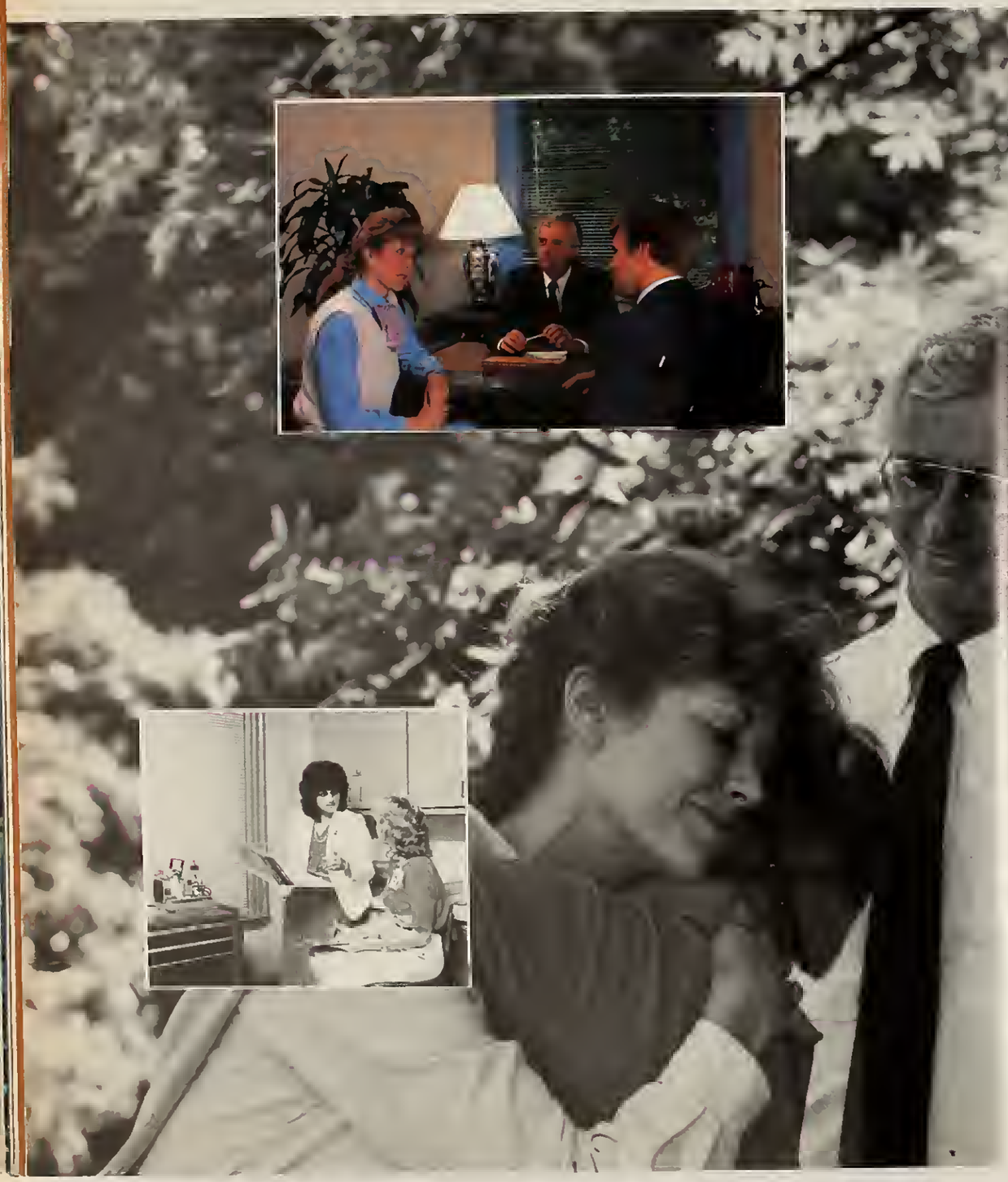

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For further information about Charter Baywood or admission procedures, contact:

Medical Director: Leon Marder, M.D.
Hospital Administrator: Diana Goulet

Charter Grove Hospital

2005 Kellogg Drive
Corona, California 91720
(714) 735-2910

Beds: 86
Psychiatric Staff: 15
Programs: Adult and Adolescent Psychiatric; Adult Addictive Disease.

Other Programs: Women's Program; Eating Disorders; and Christian Psychiatric

For further information about Charter Grove or admission procedures, contact:

Medical Director: William Cohen, M.D.
Hospital Administrator: Jim Fridlington

Charter Oak Hospital

1161 East Covina Blvd.
Covina, California 91724
(213) 966-1632

Beds: 74
Psychiatric Staff: 14
Programs: Adult, Adolescent and Child Psychiatric; Adult Addictive Disease

Other Programs: Premenstrual Syndrome Clinic

For further information about Charter Oak or admission procedures, contact:

President of Medical Staff:
Adib Bitar, M.D.
Hospital Administrator: Jim Sholes

Charter Pacific Hospital

4025 West 226th St.
Torrance, California 90505
(213) 373-7733

Beds: 96
Psychiatric Staff: 36
Programs: Adolescent, Child and Young Adult Psychiatric; Adult and Adolescent Addictive Disease

Other Programs: Pediatric Neuro/Development Diagnostic Unit; Charter Clinic, in Santa Ana, offers Neuropsychological child and adolescent services.

For further information about Charter Pacific or admission procedures, contact:

Director of Adolescent Unit:
Michael J. Levine, M.D.
Hospital Administrator: Jim Hackett

CHARTER MEDICAL CORPORATION

(Continued from Page 462)

22.5 hrs. Fee: $100. Contact: Steven Black, MD (415) 428-5815.

PSYCHIATRY

April 27-28—**The Cutting Edge 1985—Clinical Applications of Kohut's Theories on Narcissism.** UCSD. Saturday-Sunday. 12.5 hrs.

RADIOLOGY

April 29-May 3—**5th Annual Residents Radiology Review Course.** UCSD at Town and Country Inn, San Diego. Monday-Friday.

May 3—**Symposium on Magnetic Resonance Imaging—Current Practical Applications and Limitations.** Diagnostic Imaging Associates at Heritage Hotel, Denver. Friday. 7 hrs. Contact: DIA, (303) 761-9190. Fee: $85.

May 17-19—**10th Annual Spring Diagnostic Ultrasound Conference.** Los Angeles Radiological Society at Century Plaza Hotel, Los Angeles. Friday-Sunday. 17 hrs. Contact: Zbigniew Petrovich, MD, c/o L.A. Radiological Society, PO Box 91215, Los Angeles 90009-1215. (213) 642-0921.

May 19-25—**5th Annual Post Conference Seminar.** Los Angeles Radiological Society at Turtle Bay Hilton and Country Club, Kahuku, Oahu. Sunday-Saturday. 18 hrs. Contact: Zbigneiw Petrovich, MD, c/o Los Angeles Radiological Society, PO Box 91215, Los Angeles 90009-1215. (213) 642-0921.

June 9-12—**Advanced Echo-Doppler: 1985 and Complementary Imagina Tech.,** ACC at Sheraton Harbor Island, San Diego. Sunday-Wednesday. Contact: ACC, 9111 Old Georgetown Road, Bethesda, Md., 20814. (301) 897-5400.

SURGERY

April 24-26—**Postgraduate Course in General Surgery.** UCSF at Hilton Hotel, San Francisco. Wednesday-Thursday.

May 2-4—**Postgraduate Course in General Surgery.** UCSF at St. Francis Hotel, San Francisco. Thursday-Saturday. 15 hrs.

May 13-17—**Basic Microsurgery Training Workshop.** UCSD. Monday-Friday. 34 hrs. Fee: $1,200.

May 30-31—**14th Annual Neurosurgery and 8th Annual Neurosurgical Nurses Conference.** UCSF at San Francisco Hilton Hotel, San Francisco. Thursday-Friday. 15.5 hrs.

June 1—**General Surgery.** UCSF at Fresno. Saturday.

June 7-8—**Southwestern Regional Flap Workshop.** UCLA. Friday-Saturday. Contact: Daniel E. Gormley, MD, 412 W. Carroll, Ste. 207, Glendora, CA 91740.

June 7-8—**Prothetics/Orthotics.** UC, Davis at Beverly Garland Hotel, Sacramento. Friday-Saturday.

June 15-20—**Fingers to the Toes.** UC, Davis at Stanford Sierra Camp, Fallen Leaf Leak, CA. Saturday-Thursday.

June 17-21—**Basic Microsurgery Training Workshop.** UCSD at San Diego. Monday-Friday. 34 hrs. Fee: $1,200.

June 17-21—**Symposium on the Temporamandibular Joint.** UCSF at Maui Marriott Hotel, Maui, Hawaii. Monday-Friday. Fee: $425.

June 19-22—**Superficial Anatomy and Cutaneous Surgery.** UC, San Diego. Wednesday-Saturday. Fee: $250-$600.

OF INTEREST TO ALL PHYSICIANS

April 17-21—**Mountain Medicine: 1985.** UCD at North Lake Tahoe. Wednesday-Sunday.

April 21-26—**69th Annual Meeting, Federation of American Society for Experimental Biology.** Fed. of Am. Soc. for Experimental Biology at Anaheim Hilton, Anaheim. Sunday-Friday. Contact: FASEB, Office of Scientific Mtgs., (303) 530-7010.

April 24-28—**Annual Scientific Program and Postgraduate Course.** Pacific Coast Fertility Society at Caesars Palace, Las Vegas. Wednesday-Sunday. 23 hrs. Contact: Pacific Coast Fertility Society, 5820 Wilshire Blvd., #500, Los Angeles 90036. (213) 937-5514.

April 27—**10th Annual Reunion, Class of 1975.** UC San Diego, School of Medicine. Saturday. No charge. Contact: Ruth Johnson (619) 452-3700.

April 27-28—**13th Annual Family Practice Symposium.** Southern Permanente Group at Disneyland Hotel, Anaheim. Friday-Saturday. 11 hrs. Contact: Southern California Kaiser Permanente Group, 4747 Sunset Blvd, Los Angeles 90027.

May 3—**One Day Orthopaedics and Casting Procedures Workshop.** Continuing Medical Education Associates at Holiday Inn, Union Square, San Francisco. Friday. 7 hrs. Fee: $165. Contact: J. Shiller, CME Assoc., PO Box 84296, San Diego 92138. (619) 223-2997.

May 4-5—**The Father in Human Development.** San Francisco Psychoanalytic Institute at University of California, Davis. Saturday-Sunday. 10 hrs. Contact: San Francisco Psychoanalytic Institute, 2420 Sutter St., San Francisco 94115. (415) 563-5815.

May 4-11—**Applications in Preventive Medicine.** University of Arizona at California Wine Country. One Week. 24 hrs. Contact: Richard Paris, MD, PO Box 209, Sun Valley, ID 83353. (208) 788-4995.

(Continued on Page 470)

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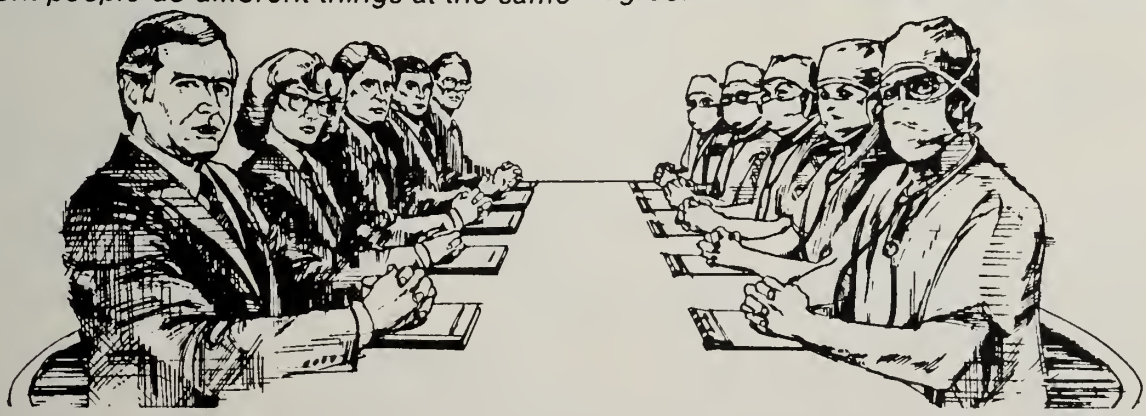

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EDWARD LOESER, MD

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CAROL F. SIMPSON, MS, PT
From the Rosalind Russell Arthritis Center, Department of Medicine, University of California, San Francisco, School of Medicine.

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SCOTT F. KRONLUND, MD, and WILLIAM R. PHILLIPS, MD, MPH
From the Department of Family Medicine, University of Washington School of Medicine, Seattle. Dr Kronlund is now affiliated with the Department of Family Practice, University of Iowa, Iowa City.

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ELLIOTT S. WOLFE, MD, and HENRY W. JONES III, MD
From the Departments of Staff Education and Medicine, Kaiser-Permanente Medical Center, Santa Clara, California. Dr Wolfe is Chief of Staff Education and Clinical Professor of Medicine and Dr Jones is Director of the Internal Medicine Residency Program and Clinical Assistant Professor of Medicine, Stanford University School of Medicine, Stanford, California.

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ROGER J. PURDY
From the Committee on Physician Supply and the Bureau of Research and Planning, Division of Research and Socioeconomics, California Medical Association, San Francisco.

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★ **Official Journal of the California Medical Association, the Idaho Medical Association, the Nevada State Medical Association, the New Mexico Medical Society, the Utah State Medical Association, the Washington State Medical Association and the Wyoming Medical Society.**

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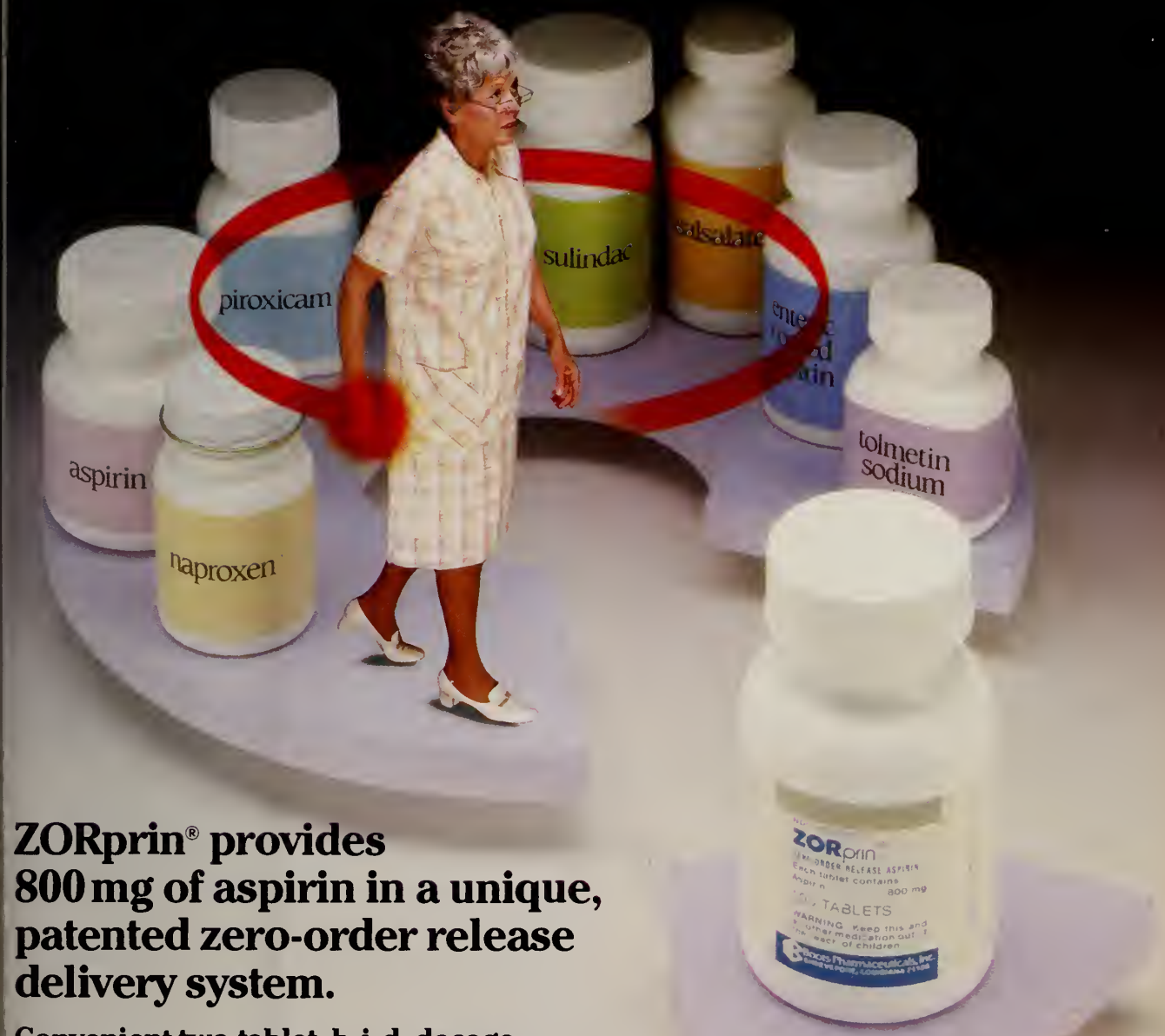

ZORprin® provides 800 mg of aspirin in a unique, patented zero-order release delivery system.

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See brief summary of prescribing information on next page.

ZORprin (aspirin) ZERO-ORDER RELEASE

Before prescribing see complete prescribing information. The following is a brief summary. ▫ **INDICATIONS AND USE**: ZORprin® is indicated for the treatment of rheumatoid arthritis and osteoarthritis. The safety and efficacy of ZORprin® have not been established in those rheumatoid arthritic patients who are designated by the American Rheumatism Association as Functional Class IV, incapacitated, largely or wholly bedridden, or confined to wheelchair, little or no self-care). ▫ **CONTRAINDICATIONS**: ZORprin® should not be used in patients known to be hypersensitive to salicylates or in individuals with the syndrome of nasal polyps, angioedema, bronchospastic reactivity to aspirin, renal or hepatic insufficiency, hypoprothrombinemia or other bleeding disorders. ZORprin® is not recommended for children under 12 years of age; it is contraindicated in all children with fever accompanied by dehydration. ▫ **WARNINGS**: ZORprin® should be used with caution when anticoagulants are prescribed concurrently, since aspirin may depress the concentration of prothrombin in plasma and increase bleeding time. Large doses of salicylates may have hypoglycemic action and enhance the effect of the oral hypoglycemics; concomitant use therefore is not recommended. However, if such use is necessary, dosage of the hypoglycemic agent must be reduced. The hypoglycemic action of the salicylates may also necessitate adjustment of the insulin requirements of diabetics. While salicylates in large doses have a uricosuric effect, smaller amounts may reduce the uricosuric effect of uricosuric agents. ▫ **USE IN PREGNANCY**: Aspirin can cause fetal harm when administered to pregnant women. Aspirin interferes with maternal and infant blood clotting and may lengthen the duration of pregnancy and parturition. Aspirin has produced teratogenic effects and increases the incidence of stillbirths and neonatal deaths in animals. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Aspirin should not be taken during the last 3 months of pregnancy. ▫ **PRECAUTIONS**: Appropriate precautions should be taken in prescribing ZORprin® for patients who are known to be sensitive to aspirin or salicylates. Particular care should be used when prescribing this medication for patients with erosive gastritis, peptic ulcer, mild diabetes or gout. As with all salicylate drugs, caution should be exercised in prescribing ZORprin® for those patients with bleeding tendencies or those on anticoagulant drugs. Large doses of salicylates should be avoided in patients with clear evidence of carditis. In order to avoid exacerbation of disease or adrenal insufficiency, patients who have been on prolonged corticosteroid therapy should have their therapy tapered slowly rather than discontinued abruptly when ZORprin® (aspirin) is made a part of the treatment program. Patients receiving large doses of aspirin and/or prolonged therapy may develop mild salicylate intoxication (salicylism) that may be reversed by reduction in dosage. Salicylates can produce changes in thyroid function tests. Salicylates should be used with caution in patients with severe hepatic damage, preexisting hypoprothrombinemia, Vitamin K deficiency and in those undergoing surgery. Since aspirin release from ZORprin® is pH dependent, it may change in those conditions where the gastric pH has been increased via antacids, gastric secretion inhibitors or surgical procedures. ▫ **ADVERSE REACTIONS**: **Hematologic**: Aspirin interferes with blood clotting. Patients with a history of blood coagulation defects or receiving anti-coagulant drugs or with severe anemia should avoid ZORprin®. Aspirin used chronically may cause a persistent iron deficiency anemia. **Gastrointestinal**: Aspirin may potentiate peptic ulcer, and cause stomach distress or heartburn. Aspirin can cause an increase in occult bleeding and in some patients massive gastrointestinal bleeding. However, the greatest release of active drug from ZORprin® is designed to occur in the small intestine over a period of time. This has resulted in less symptomatic gastrointestinal side effects. **Allergic**: Allergic and anaphylactic reactions have been noted when hypersensitive individuals have taken aspirin. The most common allergic reaction to aspirin is the induction of bronchospasm with asthma-like symptoms. Other reactions are hives, rash, angioedema, as well as rhinitis and nasal polyps. Fatal anaphylactic shock, while not common, has been reported. **Central Nervous System**: Taken in overdoses, aspirin provides stimulation which may be manifested by tinnitus. Following initial stimulation, depression of the central nervous system may be noted. **Renal**: Aspirin may rarely cause an increase in the severity of chronic kidney disease. **Hepatic**: High doses of aspirin have been reported to produce reversible hepatic dysfunction. ▫ **OVERDOSAGE**: Overdosage, if it occurs, would produce the usual symptoms of salicylism: tinnitus, vertigo, headache, confusion, drowsiness, sweating, hyperventilation, vomiting or diarrhea. Treatment for mild intoxication: emptying the stomach with an emetic, or gastric lavage with 5% sodium bicarbonate. Individuals suffering from severe intoxication should, in addition, have forced diuresis by intravenous infusions of saline and sodium bicarbonate or sodium lactate; dextrose solution. In extreme cases, hemodialysis or peritoneal dialysis may be required. ▫ **HOW SUPPLIED**: ZORprin® tablets 800 mg., plain, white capsule-shaped tablets. Bottles of 100 tablets. ▫ **CAUTION**: Federal Law prohibits dispensing without prescription. Manufactured and distributed by: Boots Pharmaceuticals, Inc. Shreveport, LA., 71106 USA

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6540 LINE AVENUE, P.O. BOX 6750
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CONTINUING MEDICAL EDUCATION

(Continued from Page 466)

May 5—**One Day Orthopaedics and Casting Procedures Workshop.** Continuing Medical Education Associates at Grand Hotel, Anaheim. Sunday. 7 hrs. Fee: $165. Contact: J. Shiller, CME Assoc., PO Box 84296, San Diego 92138. (619) 223-2997.

May 11-17—**San Francisco Orthopaedic Review—1985.** UCSF at Golden Gateway Holiday Inn, San Francisco. Tuesday-Sunday. 41 hrs.

May 15-17—**Child Abuse: Systems of Intervention.** UCD at Holiday Inn Holidome, Sacramento. Friday-Sunday.

May 21-24—**6th Annual Verne T. Inman Lectureship and 20th Annual Scientific Program.** UCSF at San Francisco. Tuesday-Friday. 14 hrs.

May 19-23—**Current Concepts in Primary Care: 12th Annual Family Practice Refresher Course.** UCD at Napa Valley. Sunday-Thursday.

May 30—**New in Vitro Assays for Allergen Specific IgE and IgG 4 Antibodies.** UCD at Hilton Hotel, Los Angeles. Thursday. Contact: Georges M. Halpern, MD, Division of Rheumatology/Allergy, UCD.

June 5-9—**28th Annual Clinical Conference and 3rd Annual Training Institute.** Northern California Pyschotherapy Society at Asilomar, Pacific Grove. Wednesday-Sunday. 17 hrs. Contact: Northern California Psychotherapy Society, 188 Gravatt Drive, Berkeley 94705.

June 6-7—**Occupational and Env. Medical Symposium.** UC, Davis at Beverly Garland Hotel, Sacramento. Thursday-Friday.

June 6-9—**California Society of Anesthesiologists Annual Scientific Meeting** at Hilton Hotel, San Francisco. Thursday-Sunday. 17 hrs. Contact: CSA, 100 S. Ellsworth Ave., Ste. 806, San Mateo 94401. (415) 348-1407.

June 14-16—**29th Annual Postgraduate Symposium Update 1985.** San Diego Academy of Family Physicians at Hotel Del Coronado, Coronado. Friday-Sunday. Contact: San Diego Acad. of Family Physicians, 2834 Levante St., La Costa 92008. (619) 436-0981.

June 17-22—**The UCI Family Practice Refresher Course.** UCI at Westin South Coast Plaza, Long Beach. Monday-Saturday. 58 hrs.

June 29-30—**7th Annual Symposium on Toxicological Emergencies.** UCSF at Cathedral Hill Hotel, San Francisco. Saturday-Sunday. Fee: $210.

June 30—**Personality and Disease: The Emerging Field of Psychoneuro-immunology.** UCSD at University of California, Santa Barbara. Sunday. 6 hrs.

(Continued on Page 474)

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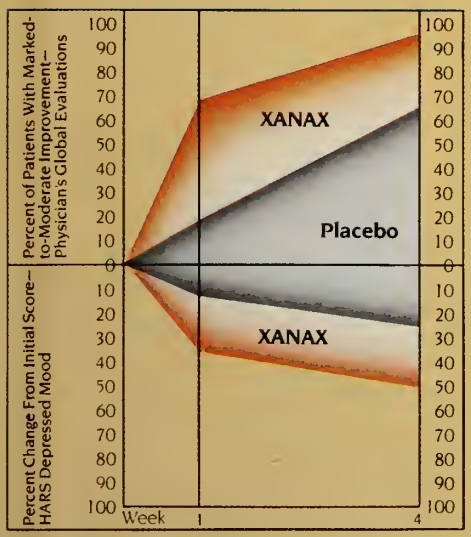
Percent of Patients With Marked-to-Moderate Improvement–Physician's Global Evaluations
Percent Change From Initial Score–HARS Depressed Mood
100 90 80 70 60 50 40 30 20 10 0
10 20 30 40 50 60 70 80 90 100
XANAX
Placebo
XANAX
Week
1
4

In a recent clinical study[1] of 83 geriatric patients with clinical anxiety, 73% were diagnosed as having symptoms of depressed mood.

XANAX is well suited for therapy because it demonstrates greater efficacy than placebo in reducing the Hamilton Anxiety Rating Scale Total Score and individual items including depressed mood (see Figure).

With clinical advantages for geriatric patients.

- **Rapidly relieves** the symptoms of anxiety
- **Rapidly relieves** associated depressed mood
- **Well tolerated**—mild, transient drowsiness, the most commonly reported side effect the first week of therapy, shows a marked decrease thereafter and is not significantly different from that of placebo
- **Does not cause** cardiotoxicity
- **Specific geriatric dosage**—0.25 mg, two or three times daily

1. Cohn JB. Double-blind safety and efficacy comparison of alprazolam and placebo in the treatment of anxiety in geriatric patients. *Curr Ther Res* 1984;35(1):100-112.

Xanax® 0.25 mg Tablets
alprazolam Ⓒ IV

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Kalamazoo, Michigan 49001 USA

Please see next page for brief summary of prescribing information.

XANAX® Tablets
(alprazolam) ℞

CONTRAINDICATIONS
Patients with sensitivity to this drug or other benzodiazepines and in acute narrow angle glaucoma

WARNINGS
Not of value in psychotic patients. Caution patients against hazardous occupations requiring complete mental alertness and about the simultaneous ingestion of alcohol and other CNS depressant drugs.

Benzodiazepines can cause fetal harm in pregnant women. Warn patients of the potential hazard to the fetus. Avoid during the first trimester.

PRECAUTIONS
General: The dosage of XANAX Tablets should be reduced or withdrawn gradually, since withdrawal seizures have been reported upon abrupt withdrawal. If XANAX is combined with other psychotropics or anticonvulsant drugs, consider drug potentiation. (See Drug Interaction section.) Exercise the usual precautions regarding size of the prescription for depressed or suicidal patients. In elderly and debilitated patients, use the lowest possible dosage. (See Dosage and Administration.) Observe the usual precautions in treating patients with impaired renal or hepatic function.

Information for Patients: Alert patients about: (a) consumption of alcohol and drugs, (b) possible fetal abnormalities, (c) operating machinery or driving, (d) not increasing dose of the drug due to risk of dependence, (e) not stopping the drug abruptly. *Laboratory Tests:* Not ordinarily required in otherwise healthy patients. *Drug Interactions:* Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistamines, ethanol and other CNS depressants. Pharmacokinetic interactions with benzodiazepines have been reported. *Drug/Laboratory Test Interactions:* No consistent pattern for a specific drug or specific test. *Carcinogenesis, Mutagenesis, Impairment of Fertility:* No carcinogenic potential or impairment of fertility in rats. *Pregnancy:* See Warnings. *Nonteratogenic Effects:* The child born of a mother on benzodiazepines may be at some risk for withdrawal symptoms and neonatal flaccidity. *Labor and Delivery:* No established use. *Nursing Mothers:* Benzodiazepines are excreted in human milk. Women on XANAX should not nurse. *Pediatric Use:* Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS
Side effects are generally observed at the beginning of therapy and usually disappear with continued medication. In the usual patient, the most frequent side effects are likely to be an extension of the pharmacological activity of XANAX, e.g., drowsiness or lightheadedness.

Central nervous system: Drowsiness, lightheadedness, depression, headache, confusion, insomnia, nervousness, syncope, dizziness, akathisia, and tiredness/sleepiness.

Gastrointestinal: Dry mouth, constipation, diarrhea, nausea/vomiting, and increased salivation.

Cardiovascular: Tachycardia/palpitations, and hypotension.

Sensory: Blurred vision.

Musculoskeletal: Rigidity and tremor.

Cutaneous: Dermatitis/allergy.

Other side effects: Nasal congestion, weight gain, and weight loss.

In addition, the following adverse events have been reported with the use of anxiolytic benzodiazepines: dystonia, irritability, concentration difficulties, anorexia, loss of coordination, fatigue, sedation, slurred speech, jaundice, musculoskeletal weakness, pruritus, diplopia, dysarthria, changes in libido, menstrual irregularities, incontinence and urinary retention.

Paradoxical reactions such as stimulation, agitation, increased muscle spasticity, sleep disturbances, and hallucinations may occur. Should these occur, discontinue the drug.

During prolonged treatment, periodic blood counts, urinalysis, and blood chemistry analysis are advisable. Minor EEG changes, of unknown significance, have been observed.

DRUG ABUSE AND DEPENDENCE
Physical and Psychological Dependence: Withdrawal symptoms have occurred following abrupt discontinuance of benzodiazepines. Withdrawal seizures have occurred upon rapid decrease or abrupt discontinuation of therapy. In all patients dosage should be gradually tapered under close supervision. Patients with a history of seizures or epilepsy should not be abruptly withdrawn from XANAX. Addiction-prone individuals should be under careful surveillance. *Controlled Substance Class:* XANAX is a controlled substance and has been assigned to schedule IV.

DOSAGE AND ADMINISTRATION
The usual starting dose is 0.25 to 0.5 mg, t.i.d. Maximum total daily dose is 4 mg. In the elderly or debilitated, the usual starting dose is 0.25 mg, two or three times daily. Reduce dosage gradually when terminating therapy, by no more than one milligram every three days.

CAUTION: FEDERAL LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION

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CONTINUING MEDICAL EDUCATION

(Continued from Page 470)

ALASKA

June 5-8—**Alaska State Medical Association Convention.** Haines. Wednesday-Saturday. Contact: ASMA, 4107 Laurel St., Anchorage 99504. (907) 562-2662.

IDAHO

July 24-27—**Idaho Medical Association Annual Meeting.** Sun Valley. Wednesday-Saturday. Contact: IMA, PO Box 2668, Boise 83701. (208) 344-7888.

MONTANA

April 17-19—**Internal Medicine Review.** University of Washington at Great Falls, Billings, Missoula. Wednesday-Friday. Contact: U/W School of Medicine, Div. of CME-50, Seattle, WA 98195. (206) 543-1050.

May 22-24—**Internal Medicine Review.** University of Washington at Great Falls, Billings, Missoula. Wednesday-Friday. Contact: U/W School of Medicine, Div. of CME-50, Seattle, WA 98195. (206) 543-1050.

NEW MEXICO

Information, requests for accreditation and items to be listed should be sent to the chairman of the CME Committee, New Mexico Medical Society, 303 San Mateo NE, Suite 204, Albuquerque, NM 87108 at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 266-7868.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

April 26-27—**Behavioral and Attitudinal Forces in Clinical Medicine.** Albuquerque. Friday-Saturday.

(Continued on Page 476)

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(Continued from Page 474)

Marriott Hotel. 14 hrs. AMA Cat. I. Contact: Office of CME, Lovelace Medical Center, 5400 Gibson SE, Albuquerque 87108. (505) 262-7353.

May 1-3—**New Mexico Medical Society Annual Meeting.** Albuquerque. Wednesday-Friday. Marriott. 9 hrs. AMA Cat. I. Contact: New Mexico Medical Society, 303 San Mateo NE, Suite 204, Albuquerque 87108. (505) 266-7868.

May 16-18—**UNM Neurology '85: New Approaches to Common Problems.** Albuquerque. Thursday-Saturday. AMFAC Hotel. AMA Cat. I. Contact: Office of CME, UNM SOM, Albuquerque 87131. (505) 277-3942.

May 31-June 1—**Cancer Update '85.** Albuquerque. Friday-Saturday. AMFAC Hotel. AMA Cat. I. Contact: Office of CME, UNM SOM, Albuquerque 87131. (505) 277-3942.

June 1-9—**The Body in Analysis.** Abiquiu. Saturday-Sunday. The Ghost Ranch. 36 hrs. NM Category I. Contact: Secretary, Ghost Ranch Conference, PO Box 417, Wilmette, IL 60091. (312) 256-7551.

June 11-14—**Medicolegal Investigation of Death.** Albuquerque. Tuesday-Friday. AMA Cat. I. AMFAC Hotel. Contact: Office of CME, UNM SOM, Albuquerque 87131. (505) 277-3942.

July 11-13—**General Surgical Update.** Albuquerque. Thursday-Saturday. Marriott Hotel. AMA Cat. I. Contact: Office of CME, UNM SOM, Albuquerque 87131. (505) 277-3942.

July 11-13—**Annual Meeting—New Mexico Ophthalmological Society.** Location to be announced. Thursday-Saturday. Contact: John M. Mezoff, MD, 508 Cabezon Court, Gallup 87301.

July 15-18—**28th Annual Ruidoso Family Practice Seminar.** Mescalero. Monday-Thursday. Inn of the Mountain Gods. 20 hrs. AMA Cat. 1 and AAFP Prescribed Credit. Contact: NM Chapter, AAFP, PO Box 23070, Albuquerque 87192. (505) 298-5300.

OREGON

The following list of continuing medical offerings in the state of Oregon is compiled by the Oregon Medical Association's Council on Medical Education. If you wish to submit information regarding future postgraduate courses, please submit the information to James A. Kronenberg, Associate Executive Director, Oregon Medical Association, 5210 SW Corbett Ave., Portland, OR 97201, or phone (503) 226-1555.

MEDICAL GRAND ROUNDS

Douglas Community Hospital, 738 West Harvard Avenue, Roseburg 97470:

Every Monday, 12:30 p.m. Contact: Robert A. Driver, MD, Douglas Community Hospital, 738 West Harvard Avenue, Roseburg, OR 97470. (503) 673-6641.

Emanuel Hospital, 2801 N. Gantenbein Street, Portland 97227:

Every Friday, 8:00 a.m. to 9:00 a.m. **Medical Grand Rounds.** Contact: Philipa McClure, Emanuel Hospital, 2801 N. Gantenbein Street, Portland, OR 92227. (505) 280-3200.

Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland 97210:

Every Wednesday, 8:00 a.m. to 9:00 a.m. **Medicine Grand Rounds.** Nursing Education Building, Room 110. Contact: Department of Medicine, Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland, OR 97201. (503) 229-7454.

Providence Medical Center, 4805 NE Glisan, Portland 97213:

Every Wednesday, 8:00 a.m. **Medical Grand Rounds.** Contact: Richard Wernick, MD, Providence Medical Center, 4805 NE Glisan, Portland, OR 97213. (503) 230-6085.

Sacred Heart General Hospital, 1200 Alder Street, Eugene, OR 97440:

Every Tuesday, 8:00 a.m. to 9:00 a.m. **Medical Grand Rounds.** Hospital Auditorium. Contact: Medical Education Committee. PO Box 10905, Eugene, OR 97440.

Salem Hospital, 665 Winter Street SE, Salem 97301:

First and third Thursday of each month 7:15 a.m. to 8:15 a.m. **Medical Live Audit Conference.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter Street SE, Salem, OR 97301. (503) 370-5339.

Every Friday, 7:30 a.m. to 8:30 a.m. **Friday Grand Rounds.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter Street SE, Salem, OR 97301. (503) 370-5339.

St. Vincent Hospital & Medical Center, 9205 SW Barnes Road, Portland 97225:

(Continued on Page 484)

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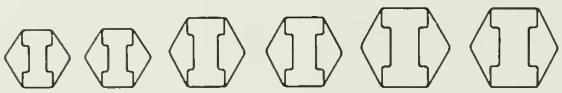

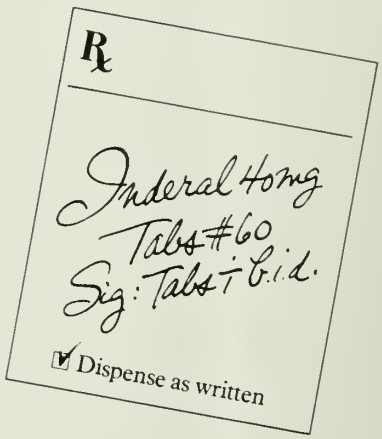

BRIEF SUMMARY (FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE CIRCULAR.)

INDERAL® (propranolol hydrochloride) Tablets

CONTRAINDICATIONS

INDERAL is contraindicated in 1) cardiogenic shock 2) sinus bradycardia and greater than first degree block, 3) bronchial asthma, 4) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL

WARNINGS

CARDIAC FAILURE Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta blockade may precipitate more severe failure. Although beta blockers should be avoided in overt congestive heart failure, if necessary they can be used with close follow-up in patients with a history of failure who are well compensated and are receiving digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle.

IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE continued use of beta blockers can, in some cases, lead to cardiac failure. Therefore, at the first sign or symptom of heart failure, the patient should be digitalized and/or treated with diuretics, and the response observed closely or INDERAL should be discontinued (gradually, if possible).

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following abrupt discontinuance of INDERAL therapy. Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced over at least a few weeks and the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)— PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

MAJOR SURGERY The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

INDERAL, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in starting and maintaining the heartbeat has also been reported with beta blockers.

DIABETES AND HYPOGLYCEMIA Beta-adrenergic blockade may prevent the appearance of certain premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia in labile insulin-dependent diabetes. In these patients, it may be more difficult to adjust the dosage of insulin.

THYROTOXICOSIS Beta blockade may mask certain clinical signs of hyperthyroidism. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

PRECAUTIONS

General Propranolol should be used with caution in patients with impaired hepatic or renal function. INDERAL is not indicated for the treatment of hypertensive emergencies.

Beta-adrenoreceptor blockade can cause reduction of intraocular pressure. Patients should be told that INDERAL (propranolol hydrochloride) may interfere with the glaucoma screening test. Withdrawal may lead to a return of increased intraocular pressure.

Clinical Laboratory Tests Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

DRUG INTERACTIONS Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if INDERAL is administered. The added catecholamine-blocking action may produce an excessive reduction of resting sympathetic nervous activity which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In 18-month studies in both rats and mice, employing doses up to 150 mg/kg/day, there was no evidence of significant drug-induced toxicity. There were no drug-related tumorigenic effects at any of the dosage levels. Reproductive studies in animals did not show any impairment of fertility that was attributable to the drug.

Pregnancy Pregnancy Category C. INDERAL has been shown to be embryotoxic in animal studies at doses about 10 times greater than the maximum recommended human dose.

There are no adequate and well-controlled studies in pregnant women. INDERAL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers INDERAL is excreted in human milk. Caution should be exercised when INDERAL is administered to a nursing woman.

Pediatric Use Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Most adverse effects have been mild and transient and have rarely required the withdrawal of therapy.

Cardiovascular bradycardia; congestive heart failure; intensification of AV block; hypotension; paresthesia of hands; thrombocytopenic purpura; arterial insufficiency, usually of the Raynaud type.

Central Nervous System Lightheadedness; mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place; short-term memory loss; emotional lability; slightly clouded sensorium; and decreased performance on neuropsychometrics.

Gastrointestinal nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis.

Allergic pharyngitis and agranulocytosis; erythematous rash, fever combined with aching and sore throat; laryngospasm and respiratory distress.

Respiratory bronchospasm.

Hematologic agranulocytosis; nonthrombocytopenic purpura; thrombocytopenic purpura.

Auto-Immune In extremely rare instances, systemic lupus erythematosus has been reported.

Miscellaneous alopecia; LE-like reactions; psoriasiform rashes; dry eyes; male impotence; and Peyronie's disease have been reported rarely. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been associated with propranolol.

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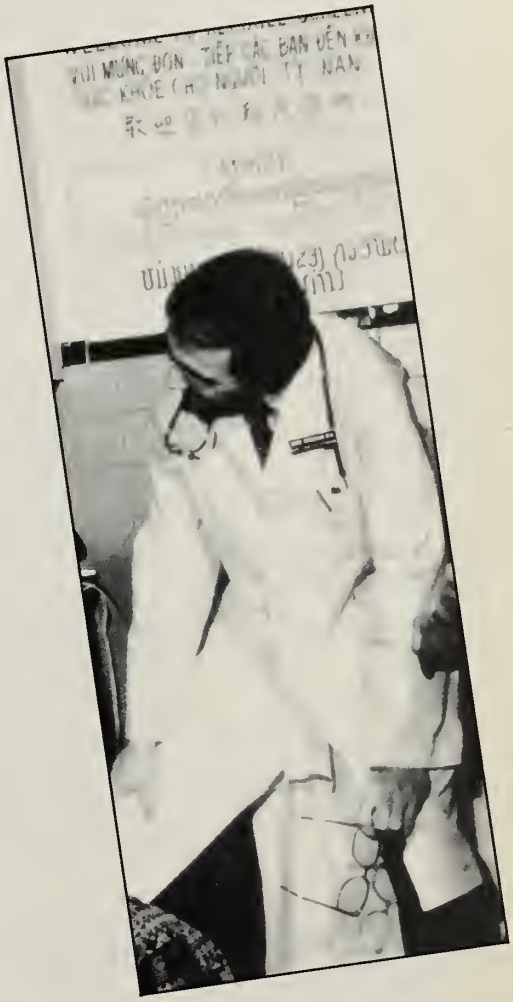

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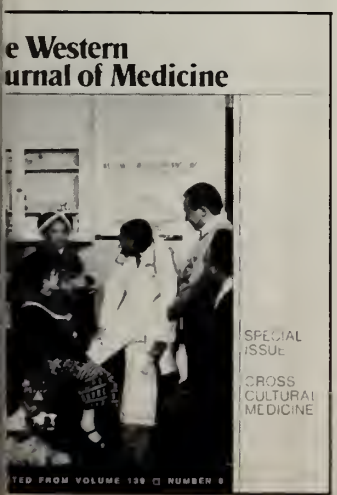

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INFORMATION FOR AUTHORS

Submitting Manuscripts

Manuscripts for consideration should be sent to the editor, Malcolm S. M. Watts, MD, 44 Gough Street, San Francisco, California 94103. The transmittal letter should designate one person as correspondent and include complete address, with ZIP code and telephone number.

In view of *The Copyright Revision Act of 1976,* transmittal letters should contain the following language: "In consideration for reviewing and editing my submission, the author(s) undersigned hereby transfers, assigns or otherwise conveys all copyright ownership to THE WESTERN JOURNAL OF MEDICINE in the event that such work is published by the journal." This statement should be signed by *all* the authors.

Authors are urged to seek clarity and succinctness in all manuscripts regardless of subject matter or format and to give close attention to syntax, grammar and spelling.

Clinical Investigation Section

Articles that authors wish to have considered for the Clinical Investigation section should be so designated in the transmittal letter. The type of articles appropriate for this section are those that describe experimental work in humans that extensively and prospectively examines scientific hypotheses relating to disease. An article describing a single case report will not normally be considered appropriate for this section.

Preparing Manuscripts

The original manuscript and *two* copies should be submitted on heavy bond paper (8½ by 11 inches, *not* erasable), typed *double-spaced throughout* (including legends, tables and references) on one side of the paper, with 1½-inch margins. Ordinarily, articles should not exceed 3,000 words (less than 15 text pages, typed double-spaced). Under exceptional circumstances only will articles longer than 4,000 words be published. Pages should be numbered consecutively, beginning with the title page.

Style

Abbreviations. Use of abbreviations should be minimized. If they are necessary, abbreviations should be spelled out at first mention, with the abbreviation itself immediately following in parentheses.

Weights and measures. All measurements should be given in metric units. English equivalents should be given parenthetically if the measurements were originally done in English units.

Temperatures. Temperature readings should be given first in Celsius, followed by the Fahrenheit equivalent in parentheses.

Drug names. If the trade name of a drug is used, the generic name should be given first, followed by the trade name in parentheses. Trade names are capitalized, generic names are not.

Title Page

Titles are best when brief and concise. The title page should include the full name of the author(s), with degrees, academic or professional titles, complete addresses and any institutional or other affiliations. The complete name and address of the person who will handle reprint requests also should appear on this page.

Abstract

The abstract (approximately 150 words) should be a short summary, saying in brief what is said at length in the body of the article—rather than such and such "is discussed," "is presented" or "was investigated."

Tables and Figures

Tables

Each table should be typed on a separate sheet of paper, be numbered consecutively in Arabic numerals, have a brief descriptive title and have its position indicated in the text.

Illustrations (Figures)

Three sets of clear, unmounted black and white glossy prints of figures should be submitted (preferably 5 by 7 inches, but no larger than 8½ by 11 inches). For line drawings, original artwork or glossy prints are acceptable. Illustrations should be numbered consecutively in Arabic numerals and their position indicated in the text. Figure number, first author's name and top of the photo should be shown on the reverse side of each illustration. Recognizable photographs of patients are to be masked and written permission for publication obtained from the patients.

Legends

All legends for figures should be typed together on a separate sheet of paper. Magnification and stain for photomicrographs should be indicated in parentheses.

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References

References should be limited to those cited in the text. They must be typed double-spaced and numbered consecutively as they appear in the manuscript. (See examples below for style.) Abbreviations of journal titles should conform to those used in *Index Medicus.*

Journal Articles

Note handling of multiple authorship. If more than three authors are listed as contributors, use "et al" to designate those names after the first three. Also note capitalization, punctuation, mention of inclusive page numbers and year of publication. Separate the subtitle from the title by either a dash or a colon. Use colon *only* if it appears in the original citation.

1. Jones JS, Anderson HW, Johnson DW, et al: The athletic heart revisited—Sudden death of a 28-year-old athlete. JAMA 1978; 292:444-456

2. Graybill JR, Alford RH, Smith RG, et al: Cell-mediated immunity in cryptococcosis: A brief review. Cell Immunol 1978; 7:76-79

Books

Note handling of "edition," "editor(s)," and "volume," as well as appropriate sequence of reference information and capitalization of chapters and titles.

3. Berne EJ, Smith TL: Role playing in therapy, chap 2, Principles of Group Therapy. New York, Oxford University Press, 1966, pp 35-51 *(author of chapter same as author of book)*

4. Munsung JM: The role of drugs, chap 2, *In* Brest AN, Mayer JH (Eds): Hypertension—Vol 2, Therapy, 2nd Ed. Springfield, Ill, Charles C Thomas, 1961, pp 456-479 *(author of chapter different from authors of book)*

Pamphlets, Monographs or Books With No Given Author

5. AMA Department of Drugs: AMA Drug Evaluation, 3rd Ed. Littleton, Mass, Publishing Sciences Group, 1977 *(corporate author)*

6. Compilation of Standard Definitions, 3rd Ed. Philadelphia, American Society for Testing and Materials, 1976 *(no given author; give name and place of publisher)*

Articles in Press or Accepted for Publication

Any article accepted for publication should include the name of the journal (appropriately abbreviated) in which it will appear, and the phrase "in press" or "accepted for publication" in place of the date of publication.

Personal Communications and Unpublished Data

This information should *not* be included in the reference list but should be given in parentheses in the body of the text. Date of communication, whether it was personal or written, and the person's name, highest academic degree and professional affiliation should be provided.

Acknowledgments

It is the policy of the *WJM* not to print acknowledgments, the feeling being that if a person has contributed enough to a paper to be mentioned, he or she should be included among the authors, or the contribution should be mentioned in the body of the paper or in a footnote.

Correspondence

Brief manuscripts commenting on articles that have appeared in the journal, containing information of interest to physicians or discussing issues of the day will be considered for publication. Very short reports of cases, clinical experience, clinical studies, adverse effects and the like also will be considered. Items for the Correspondence section should not exceed 600 words and should have no more than five bibliographic references and one figure or table.

Author Responsibility

Authors are responsible for all statements made in articles. Manuscripts are considered for publication with the explicit understanding that they are original, have not been published previously and are not simultaneously under consideration by any other publication.

All accepted manuscripts are subject to copy editing, and authors are sent edited galleys for approval. No changes will be made after the final, edited version has been approved by the author.

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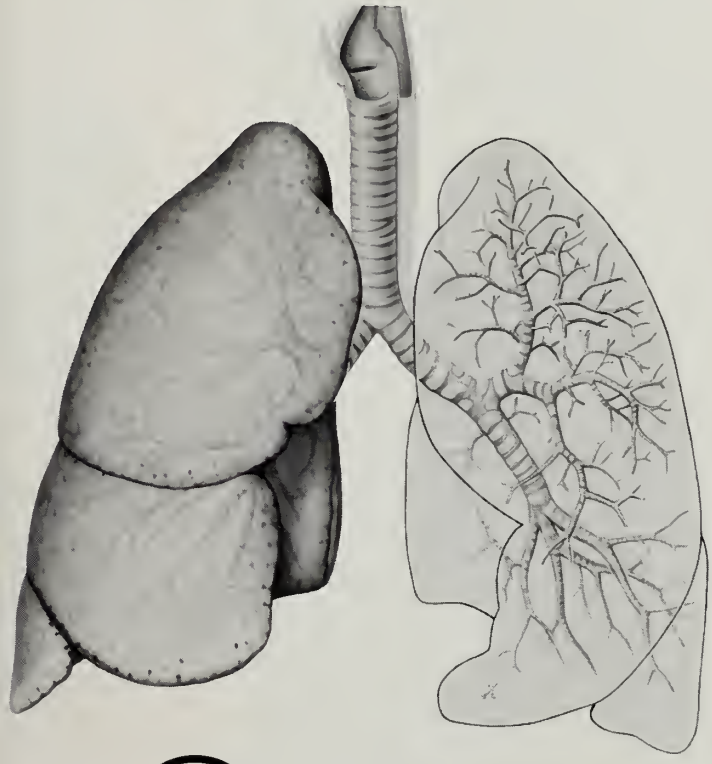

Ceclor®
cefaclor
250-mg Pulvules® t.i.d.

offers effectiveness against the major causes of bacterial bronchitis

H. influenzae, H. influenzae, S. pneumoniae, S. pyogenes
(ampicillin-susceptible) (ampicillin-resistant)

Brief Summary: Consult the package literature for prescribing information.

Indications and Usage: Ceclor* (cefaclor, Lilly) is indicated in the treatment of the following infections when caused by susceptible strains of the designated microorganisms:

Lower respiratory infections, including pneumonia caused by *Streptococcus pneumoniae (Diplococcus pneumoniae), Haemophilus influenzae*, and *S. pyogenes* (group A beta-hemolytic streptococci).

Appropriate culture and susceptibility studies should be performed to determine susceptibility of the causative organism to Ceclor.

Contraindication: Ceclor is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

Warnings: IN PENICILLIN-SENSITIVE PATIENTS, CEPHALOSPORIN ANTIBIOTICS SHOULD BE ADMINISTERED CAUTIOUSLY. THERE IS CLINICAL AND LABORATORY EVIDENCE OF PARTIAL CROSS-ALLERGENICITY OF THE PENICILLINS AND THE CEPHALOSPORINS, AND THERE ARE INSTANCES IN WHICH PATIENTS HAVE HAD REACTIONS, INCLUDING ANAPHYLAXIS, TO BOTH DRUG CLASSES.

Antibiotics, including Ceclor, should be administered cautiously to any patient who has demonstrated some form of allergy, particularly to drugs.

Pseudomembranous colitis has been reported with virtually all broad-spectrum antibiotics (including macrolides, semisynthetic penicillins, and cephalosporins); therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with the use of antibiotics. Such colitis may range in severity from mild to life-threatening.

Treatment with broad-spectrum antibiotics alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis.

Mild cases of pseudomembranous colitis usually respond to drug discontinuance alone. In moderate to severe cases, management should include sigmoidoscopy, appropriate bacteriologic studies, and fluid, electrolyte, and protein supplementation. When the colitis does not improve after the drug has been discontinued, or when it is severe, oral vancomycin is the drug of choice for antibiotic-associated pseudomembranous colitis produced by *C. difficile*. Other causes of colitis should be ruled out.

Precautions: *General Precautions* — If an allergic reaction to Ceclor* (cefaclor, Lilly) occurs, the drug should be discontinued, and, if necessary, the patient should be treated with appropriate agents, e.g., pressor amines, antihistamines, or corticosteroids.

Prolonged use of Ceclor may result in the overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Positive direct Coombs' tests have been reported during treatment with the cephalosporin antibiotics. In hematologic studies or in transfusion cross-matching procedures when antiglobulin tests are performed on the minor side or in Coombs' testing of newborns whose mothers have received cephalosporin antibiotics before parturition, it should be recognized that a positive Coombs' test may be due to the drug.

Ceclor should be administered with caution in the presence of markedly impaired renal function. Under such conditions, careful clinical observation and laboratory studies should be made because safe dosage may be lower than that usually recommended.

As a result of administration of Ceclor, a false-positive reaction for glucose in the urine may occur. This has been observed with Benedict's and Fehling's solutions and also with Clinitest® tablets but not with Tes-Tape® (Glucose Enzymatic Test Strip, USP, Lilly).

Broad-spectrum antibiotics should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis.

Usage in Pregnancy — *Pregnancy Category B* — Reproduction studies have been performed in mice and rats at doses up to 12 times the human dose and in ferrets given three times the maximum human dose and have revealed no evidence of impaired fertility or harm to the fetus due to Ceclor* (cefaclor, Lilly). There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers — Small amounts of Ceclor have been detected in mother's milk following administration of single 500-mg doses. Average levels were D 16, D 20, D 21, and D 16 mcg/ml at two, three, four, and five hours respectively. Trace amounts were detected at one hour. The effect on nursing infants is not known. Caution should be exercised when Ceclor is administered to a nursing woman.

Usage in Children — Safety and effectiveness of this product for use in infants less than one month of age have not been established.

Adverse Reactions: Adverse effects considered related to therapy with Ceclor are uncommon and are listed below:

Gastrointestinal symptoms occur in about 2.5 percent of patients and include diarrhea (1 in 70).

Symptoms of pseudomembranous colitis may appear either during or after antibiotic treatment. Nausea and vomiting have been reported rarely.

Hypersensitivity reactions have been reported in about 1.5 percent of patients and include morbilliform eruptions (1 in 100). Pruritus, urticaria, and positive Coombs' tests each occur in less than 1 in 200 patients. Cases of serum-sickness-like reactions (erythema multiforme or the above skin manifestations accompanied by arthritis/arthralgia and, frequently, fever) have been reported. These reactions are apparently due to hypersensitivity and have usually occurred during or following a second course of therapy with Ceclor. Such reactions have been reported more frequently in children than in adults. Signs and symptoms usually occur a few days after initiation of therapy and subside within a few days after cessation of therapy. No serious sequelae have been reported. Antihistamines and corticosteroids appear to enhance resolution of the syndrome.

Cases of anaphylaxis have been reported, half of which have occurred in patients with a history of penicillin allergy.

Other effects considered related to therapy included eosinophilia (1 in 50 patients) and genital pruritus or vaginitis (less than 1 in 100 patients).

Causal Relationship Uncertain — Transitory abnormalities in clinical laboratory test results have been reported. Although they were of uncertain etiology, they are listed below to serve as alerting information for the physician.

Hepatic — Slight elevations in SGOT, SGPT, or alkaline phosphatase values (1 in 40).

Hematopoietic — Transient fluctuations in leukocyte count, predominantly lymphocytosis occurring in infants and young children (1 in 40).

Renal — Slight elevations in BUN or serum creatinine (less than 1 in 500) or abnormal urinalysis (less than 1 in 200).

[061782R]

Note: Ceclor* (cefaclor, Lilly) is contraindicated in patients with known allergy to the cephalosporins and should be given cautiously to penicillin-allergic patients.

Penicillin is the usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. See prescribing information.

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Additional information available to the profession on request from Eli Lilly and Company, Indianapolis, Indiana 46285

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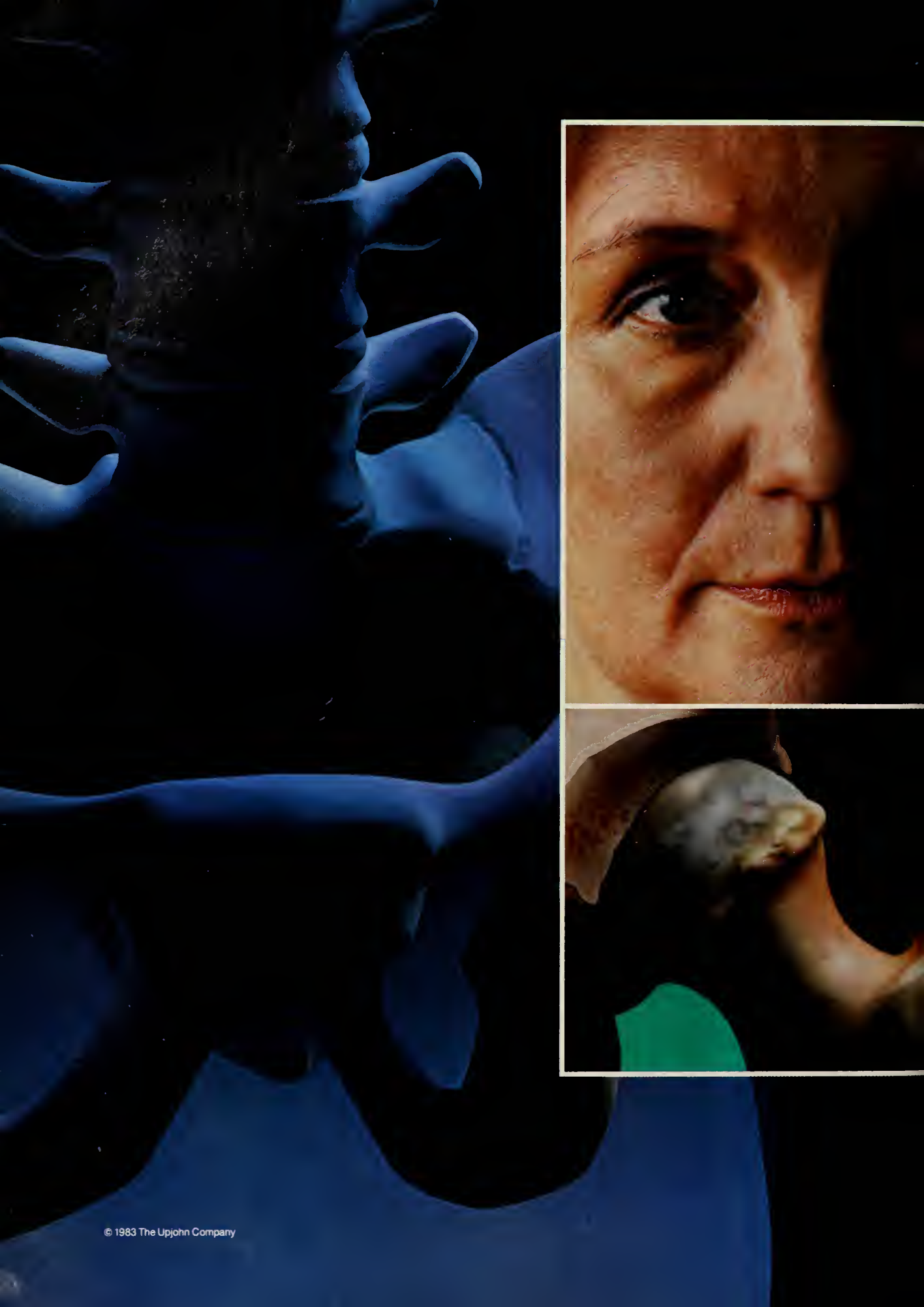

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Arthritis pain after 50

Age is no barrier to the benefits of Motrin 600 mg tablets

The pain-relieving power of *Motrin* 600 mg tablets is welcome at any age. The advantages of *Motrin* become more important as patients grow older.

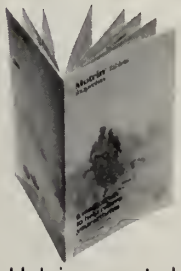
Advanced age has little or no influence on the pharmacokinetics of *Motrin*.

Motrin is as effective as indomethacin in relieving arthritis pain and inflammation. *Motrin* causes significantly fewer CNS effects and about half as many GI complaints as indomethacin.

Motrin relieves pain as effectively as a combination of aspirin 650 mg plus codeine 60 mg, as documented in analgesia studies.

Motrin has no significant effect on clotting factors in patients on coumarin-type anticoagulants in controlled studies. *Motrin* should be used with caution in persons with intrinsic coagulation defects and in those on anticoagulant therapy.

Motrin is rapidly metabolized and does not accumulate. *Motrin* provides better control of therapy, rapid response to dosage adjustment, and permits tailoring dosage to each patient's needs.



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Motrin® 600 mg TABLETS
(ibuprofen)

One tablet t.i.d.

Please turn page for a brief summary of prescribing information.

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Kalamazoo, Michigan 49001

Motrin® Tablets (ibuprofen)

Contraindications: Anaphylactoid reactions have occurred in individuals hypersensitive to *Motrin* Tablets or with the syndrome of nasal polyps, angioedema and bronchospastic reactivity to aspirin, iodides, or other nonsteroidal anti-inflammatory agents.

Warnings: Peptic ulceration and GI bleeding, sometimes severe, have been reported. Ulceration, perforation and bleeding may end fatally. An association has not been established. Use *Motrin* Tablets under close supervision in patients with a history of upper gastrointestinal tract disease, after consulting ADVERSE REACTIONS. In patients with active peptic ulcer and active rheumatoid arthritis, try nonulcerogenic drugs, such as gold. If *Motrin* Tablets are used, observe the patient closely for signs of ulcer perforation or GI bleeding.

Chronic studies in rats and monkeys have shown mild renal toxicity with papillary edema and necrosis. Renal papillary necrosis has rarely been shown in humans treated with *Motrin* Tablets.

Precautions: Blurred and/or diminished vision, scotomata, and/or changes in color vision have been reported. If these develop, discontinue *Motrin* Tablets and the patient should have an ophthalmologic examination, including central visual fields and color vision testing.

Fluid retention and edema have been associated with *Motrin* Tablets; use with caution in patients with a history of cardiac decompensation or hypertension. In patients with renal impairment, reduced dosage may be necessary. Prospective studies of *Motrin* Tablets safety in patients with chronic renal failure have not been done.

Motrin Tablets can inhibit **platelet aggregation** and prolong bleeding time. Use with caution in persons with intrinsic coagulation defects and on anticoagulant therapy.

Patients should report signs or symptoms of **gastrointestinal ulceration** or bleeding, skin rash, weight gain, or edema.

Patients on prolonged **corticosteroid therapy** should have therapy tapered slowly when *Motrin* Tablets are added.

The antipyretic, anti-inflammatory activity of *Motrin* Tablets may mask inflammation and fever.

As with other nonsteroidal anti-inflammatory drugs, borderline elevations of liver tests may occur in up to 15% of patients. These abnormalities may progress, may remain essentially unchanged, or may be transient with continued therapy. Meaningful elevations of SGPT or SGOT (AST) occurred in controlled clinical trials in less than 1% of patients. Severe hepatic reactions, including jaundice and cases of fatal hepatitis, have been reported with ibuprofen as with other nonsteroidal anti-inflammatory drugs. If liver disease develops or if systemic manifestations occur (e.g. eosinophilia, rash, etc.), *Motrin* should be discontinued.

Drug interactions. *Aspirin:* used concomitantly may decrease *Motrin* blood levels.

Coumarin: bleeding has been reported in patients taking *Motrin* and coumarin.

Pregnancy and nursing mothers: *Motrin* should not be taken during pregnancy or by nursing mothers.

Adverse Reactions: The most frequent type of adverse reaction occurring with *Motrin* is gastrointestinal of which one or more occurred in 4% to 16% of the patients.

Incidence Greater than 1% (but less than 3%)—Probable Causal Relationship

Gastrointestinal: Nausea;* epigastric pain;* heartburn;* diarrhea, abdominal distress, nausea and vomiting, indigestion, constipation, abdominal cramps or pain, fullness of GI tract (bloating and flatulence); **Central Nervous System:** Dizziness;* headache, nervousness; **Dermatologic:** Rash* (including maculopapular type), pruritus; **Special Senses:** Tinnitus; **Metabolic/Endocrine:** Decreased appetite; **Cardiovascular:** Edema, fluid retention (generally responds promptly to drug discontinuation; see PRECAUTIONS).

Incidence less than 1%—Probable Causal Relationship**

Gastrointestinal: Gastric or duodenal ulcer with bleeding and/or perforation, gastrointestinal hemorrhage, melena, gastritis, hepatitis, jaundice, abnormal liver function tests; **Central Nervous System:** Depression, insomnia, confusion, emotional lability, somnolence, aseptic meningitis with fever and coma; **Dermatologic:** Vesiculobullous eruptions, urticaria, erythema multiforme, Stevens-Johnson syndrome, alopecia; **Special Senses:** Hearing loss, amblyopia (blurred and/or diminished vision, scotomata, and/or changes in color vision) (see PRECAUTIONS); **Hematologic:** Neutropenia, agranulocytosis, aplastic anemia, hemolytic anemia (sometimes Coombs positive), thrombocytopenia with or without purpura, eosinophilia, decreases in hemoglobin and hematocrit; **Cardiovascular:** Congestive heart failure in patients with marginal cardiac function, elevated blood pressure, palpitations; **Allergic:** Syndrome of abdominal pain, fever, chills, nausea and vomiting; anaphylaxis; bronchospasm (see CONTRAINDICATIONS); **Renal:** Acute renal failure in patients with pre-existing significantly impaired renal function, decreased creatinine clearance, polyuria, azotemia, cystitis, hematuria; **Miscellaneous:** Dry eyes and mouth, gingival ulcer, rhinitis.

Incidence less than 1%—Causal Relationship Unknown**

Gastrointestinal: Pancreatitis; **Central Nervous System:** Paresthesias, hallucinations, dream abnormalities, pseudotumor cerebri; **Dermatologic:** Toxic epidermal necrolysis, photoallergic skin reactions; **Special Senses:** Conjunctivitis, diplopia, optic neuritis; **Hematologic:** Bleeding episodes (e.g., epistaxis, menorrhagia); **Metabolic/Endocrine:** Gynecomastia, hypoglycemic reaction; **Cardiovascular:** Arrhythmias (sinus tachycardia, sinus bradycardia); **Allergic:** Serum sickness, lupus erythematosus syndrome, Henoch-Schönlein vasculitis; **Renal:** Renal papillary necrosis.

Reactions occurring in 3% to 9% of patients treated with *Motrin.* (Those reactions occurring in less than 3% of the patients are unmarked.)

Reactions are classified under *"Probable Causal Relationship (PCR)"* if there has been one positive rechallenge or if three or more cases occur which might be causally related. Reactions are classified under *"Causal Relationship Unknown"* if seven or more events have been reported but the criteria for PCR have not been met.

Overdosage: In cases of acute overdosage, the stomach should be emptied. The drug is acidic and excreted in the urine so alkaline diuresis may be beneficial.

Dosage and Administration: Rheumatoid arthritis and osteoarthritis. Suggested dosage is 300, 400, or 600 mg t.i.d. or q.i.d. Do not exceed 2400 mg per day. Mild to moderate pain: 400 mg every 4 to 6 hours as necessary.

Caution: Federal law prohibits dispensing without prescription.

Motrin is a registered trademark of The Upjohn Manufacturing Company M, Barceloneta, Puerto Rico

MED B-7-S

J-3253 June 1983

Upjohn

CONTINUING MEDICAL EDUCATION

(Continued from Page 476)

First, third, fourth and fifth Wednesday of each month, 8:00 a.m. to 9:00 a.m. **Medical Grand Rounds.** Souther Auditorium. Contact: Bonnie Conger, Secretary to Dr Kenneth Melvin, St. Vincent Hospital & Medical Center, 9205 SW Barnes Road, Portland 97225. (503) 297-4411, Ext. 2230

Oregon Health Sciences University, Department of Psychiatry, Portland 97201:

Every Wednesday, 4:00 p.m. to 5:00 p.m. **Department of Psychiatry Grand Round Presentations.** Room 8B-60, University Hospital South, Oregon Health Sciences University. Contact: Dept. of Psychiatry, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8144.

Oregon Health Sciences University, Department of Medicine, Portland 97201:

Every Tuesday, 8:00 a.m. to 9:00 a.m. **Department of Medicine Grand Rounds.** U.H.S.-8B-60, Oregon Health Sciences University. Contact: Dept. of Medicine, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8607.

FAMILY PRACTICE GRAND ROUNDS

Every Wednesday, 11:00 a.m. to 12:00 Noon. **Family Practice Grand Rounds.** Family Practice Center, Oregon Health Sciences University, Portland. Contact: William A. Fisher, MD, Oregon Health Sciences University, Department of Family Practice, Portland, OR 97201. (503) 225-7590.

INTERNAL MEDICINE

May 31-June 1—**Internal Medicine Update.** Portland. Friday-Saturday. Marriott Hotel. Contact: OHSU-CME.

OF INTEREST TO ALL PHYSICIANS

May 10—**Hypertension.** Portland. Friday. OHSU Library Auditorium. Contact: OHSU-CME.

May 17—**Infectious Diseases in Clinical Practice.** Portland. Friday. OHSU Library Auditorium. Contact: OHSU-CME.

CONTACT INFORMATION

OHSU-CME—Contact: Division of Continuing Medical Education, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8700.

(Continued on Page 492)

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Books Received

Books received by THE WESTERN JOURNAL OF MEDICINE *are acknowledged in this column. Selections will be made for more extensive review in the interest of readers as space permits.*

GENERAL UROLOGY—11th Edition—Donald R. Smith, MD, Professor of Urology Emeritus, University of California, San Francisco, School of Medicine; Visiting Professor of Urology, Faculty of Medicine, Assiut University, Assiut, Egypt. Lange Medical Publications, Drawer L, Los Altos, CA 94022, 1984. 661 pages, $24.

GYNECOLOGIC CANCER—Volume 2 of CONTEMPORARY ISSUES IN CLINICAL ONCOLOGY—Edited by Arlene A. Forastiere, MD, Assistant Professor, Dept of Internal Medicine, Division of Hematology-Oncology, University of Michigan Medical Center; Chief, Oncology Section, Veterans Administration Medical Center, Ann Arbor, Michigan. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1984. 307 pages, $38.

HEMATOPOIESIS—Edited by David W. Golde, MD, Chief, Division of Hematology-Oncology, Dept of Medicine, UCLA School of Medicine, Los Angeles. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1984. 361 pages, $55.

HOW TO SURVIVE MEDICAL SCHOOL—Toni Martin, MD. Penguin Books, 40 W 23rd St, New York, NY 10010, 1984. 180 pages, $5.95 U.S.A., $6.95 CAN (paperback).

IMMUNOLOGY AND INFECTION IN THE ELDERLY—Edited by Roy A. Fox, BSc, MB, BS, MD, FRCP, FACP, FRCP(C), Professor of Medicine, Dalhousie University and Consultant Physician in Geriatrics, Camp Hill Hospital, Halifax, Nova Scotia, Canada. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1984. 379 pages $40.

LABORATORY HEMATOLOGY—Volumes 1 and 2—Edited by John A. Koepke, MD, Professor and Director, Transfusion Service and Hematology Laboratories, Dept of Pathology, Duke University Medical Center, Durham, NC. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1984. 1,257 pages, $125.

MAGIC BULLETS—Grant Fjermedal. Macmillan Publishing Company, 866 Third Ave, New York, NY 10022, 1984. 244 pages, $15.95.

***MEDICAL ECONOMICS* ENCYCLOPEDIA OF PRACTICE AND FINANCIAL MANAGEMENT**—Edited by Lawrence Farber, West Coast Financial Editor, *Medical Economics*. Medical Economics Books, Box C-779, Pratt Station, Brooklyn, NY 11205, 1985. 1,253 pages, $69.95 plus a $1.50 handling charge.

METABOLIC BONE AND STONE DISEASE—Edited by B. E. C. Nordin, MD, FRCP, FRACP, DSc, Senior Research Fellow and Clinical Professor, Endocrine Unit, Royal Adelaide Hospital, Adelaide, South Australia. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1984. 435 pages, $69.

NEW DIMENSIONS IN ANTIMICROBIAL THERAPY—Volume 1 of CONTEMPORARY ISSUES IN INFECTIOUS DISEASES—Edited by Richard K. Root, MD, Professor and Vice Chairman, Dept of Medicine, University of Washington School of Medicine, and Chief, Medical Service, VA Medical Center, Seattle, and Merle A. Sande, MD, Professor and Vice Chairman, Dept of Medicine, University of California, San Francisco, School of Medicine, and Chief, Medical Service, San Francisco General Hospital Medical Center. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1984. 350 pages, $52.

NUTRITION, HYPERTENSION AND CARDIOVASCULAR DISEASE—Ronald S. Smith. The Lyncean Press, 885 Eighth St, Gilroy, CA 95020, 1984. 210 pages, $12.95 (paperback).

PAGING DOCTORS—Messages From a Medical Journalist—David Woods, Director of Publications, Canadian Medical Association, Ottawa. Epigram Publishing, PO Box 6044, Station J, Ottawa, Ontario, Canada K2A 1T1, 1984. 178 pages, $20.

PARSONS' DISEASES OF THE EYE—Seventeenth Edition—Stephen J. H. Miller, KCVO, MD, FRCS, Consulting Ophthalmic Surgeon, St George's Hospital, London; Moorfields Eye Hospital; The National Hospital for Nervous Diseases, Queen Square. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1984. 384 pages, $35.

PATHOLOGY OF TUMOURS OF THE ORAL TISSUES—Fourth Edition—R. B. Lucas, MD, FRCP, FRCPath, FDSRCS, Emeritus Professor of Oral Pathology, University of London. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1984. 426 pages, $79.

PHYSICIAN'S GUIDE TO PROFESSIONAL AND PERSONAL ADVISERS—Warren Boroson. Medical Economics Books, Oradell, NJ 07649, 1985. 230 pages, $16.95* (paperback). *Prices are subject to change.

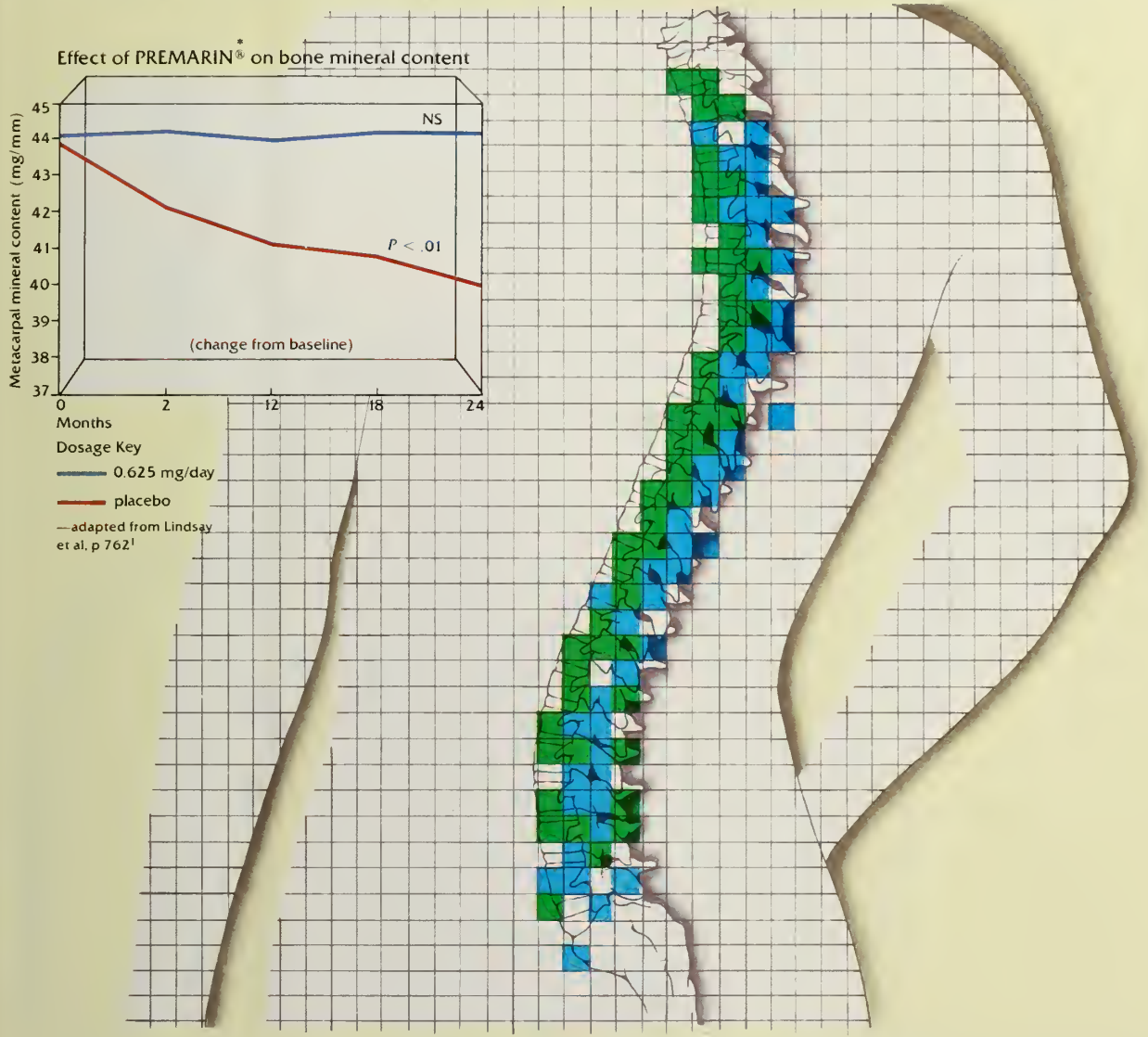
A PRACTICAL GUIDE TO CHEST IMAGING—Patricia R. Watkins, FCR, TDCR, Deputy Principal, Norfolk and Norwich School of Radiography. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1984. 260 pages, $26 (softbound).

REVIEW OF GENERAL PSYCHIATRY—Edited by Howard H. Goldman, MD, MPH, PhD, Associate Professor of Psychiatry and Director of Medical Student Education, Department of Psychiatry and Langley Porter Psychiatric Institute, University of California, San Francisco; Assistant Director, National Institute of Mental Health, Rockville, MD, and Adjunct Associate Professor of Psychiatry and Behavioral Sciences, George Washington University School of Medicine, Washington, DC. Lange Medical Publications, Drawer L, Los Altos, CA 94022, 1984. 696 pages, $24.

TAYLOR'S PRINCIPLES AND PRACTICE OF MEDICAL JURISPRUDENCE—Thirteenth Edition—Edited by A. Keith Mant, MD(Lond), FRCP, FRCPath, DMJ, Professor of Forensic Medicine, University of London; Head, Dept of Forensic Medicine, Guy's Hospital, London. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1984. 415 pages, $59.

TRANSPLANTATION IN THE 1980s—Recent Advances—Edited by Rex L. Jamison, MD, Professor of Medicine and Physiology; Chief, Division of Nephrology, Stanford University School of Medicine. Praeger Publishers, 521 Fifth Ave, New York, NY 10175, 1984. 112 pages, $24.95.

POSTMENOPAUSAL BONE LOSS THAT INCAPACITATES



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PREMARIN®
(CONJUGATED ESTROGENS TABLETS, U.S.P.)

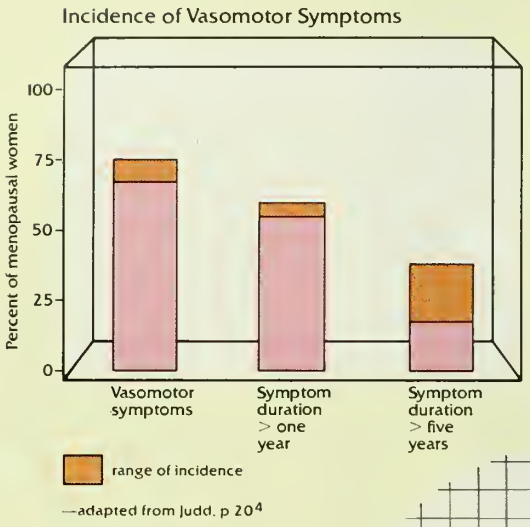
0.3 mg 0.625 mg 0.9 mg 1.25 mg 2.5 mg

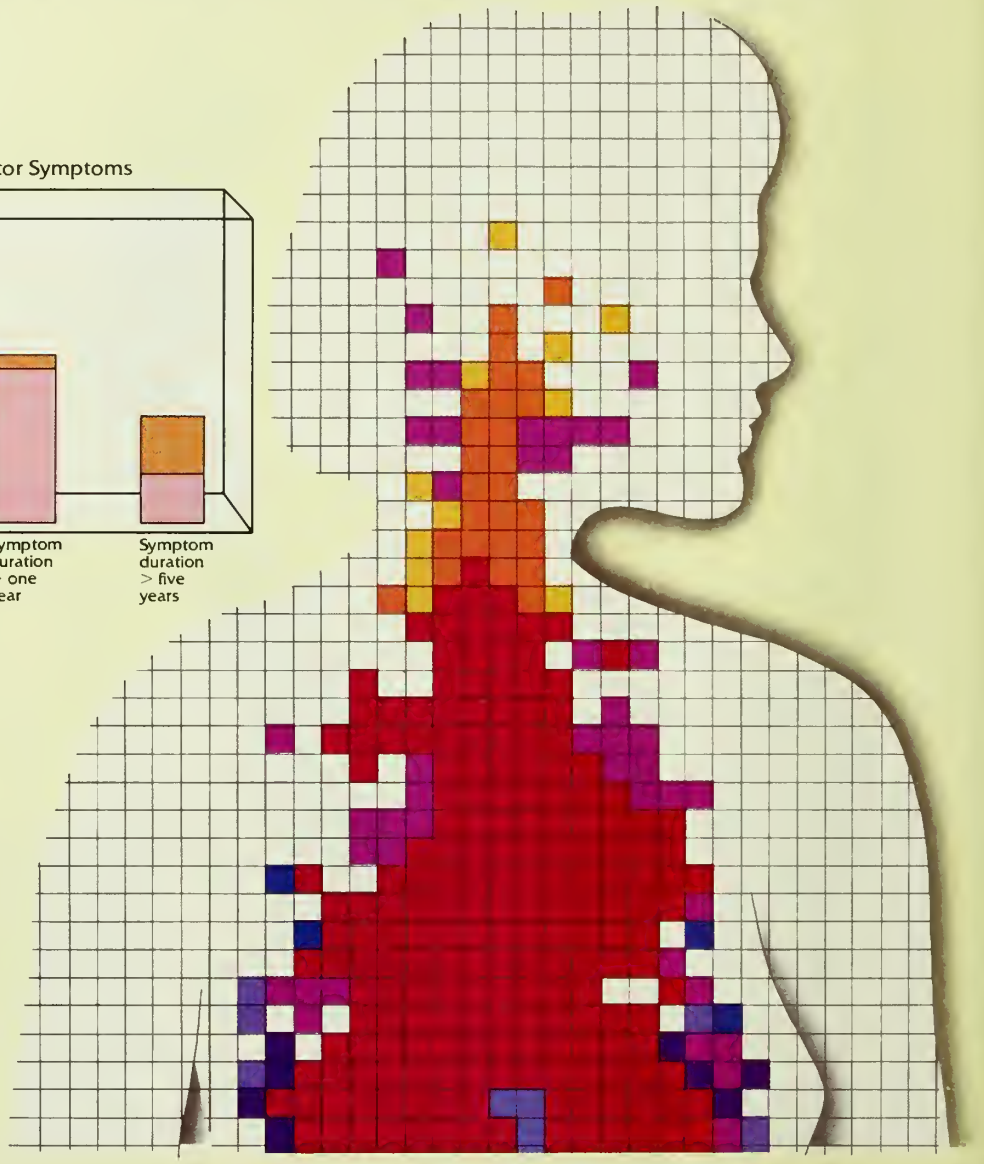
The appearance of these tablets is a trademark of Ayerst Laboratories

*Conjugated Estrogens Tablets have been evaluated as probably effective for estrogen-deficiency-induced osteoporosis.

Please see last page for brief summary of full prescribing information.

VASOMOTOR SYMPTOMS THAT DEMAND INTERVENTION





PREMARIN RELIEVES MODERATE TO SEVERE VASOMOTOR SYMPTOMS

Vasomotor symptoms are the most common manifestation of the menopause, affecting up to 75% of menopausal women. Of these, 80% may suffer for more than a year and up to 50% for more than five years.[4] These symptoms can disrupt a woman's life by chronically interrupting sleep, resulting in anxiety and irritability.

In a study of postmenopausal women suffering severe episodes of cutaneous flushing, symptoms improved markedly after administration of estrogen[5]—the treatment of choice for moderate to severe vasomotor symptoms.[6] The estrogen of choice is PREMARIN, the most widely prescribed estrogen for over 40 years. PREMARIN (Conjugated Estrogens Tablets, U.S.P.) relieves moderate to severe vasomotor symptoms of the natural menopause, as well as the acute and often severe symptoms of surgical menopause.

PREMARIN®

(CONJUGATED ESTROGENS TABLETS, U.S.P.)

0.3 mg 0.625 mg 0.9 mg 1.25 mg 2.5 mg

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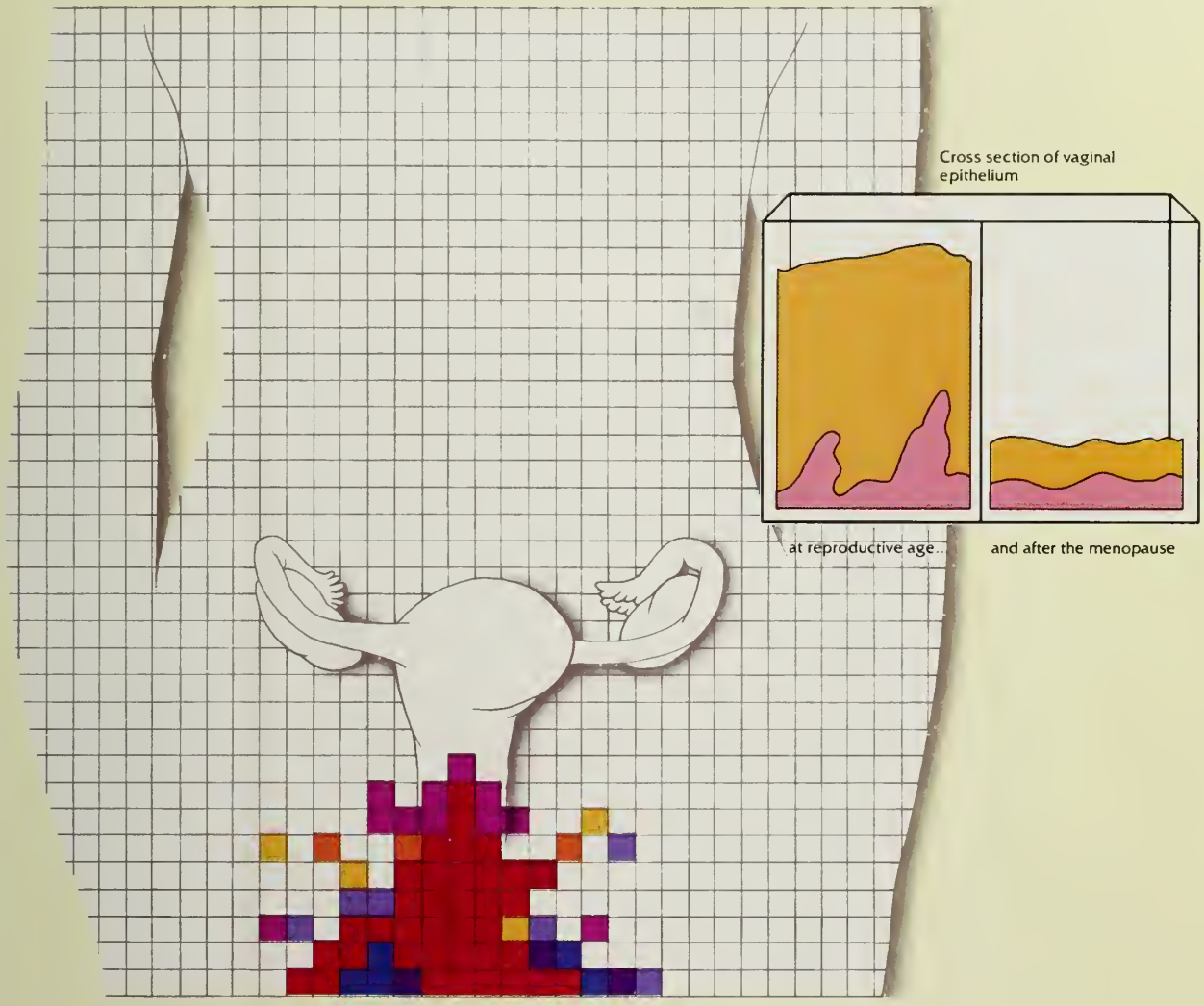
Please see last page for brief summary of full prescribing information.

VAGINAL ATROPHY THAT INTERFERES WITH SEXUALITY



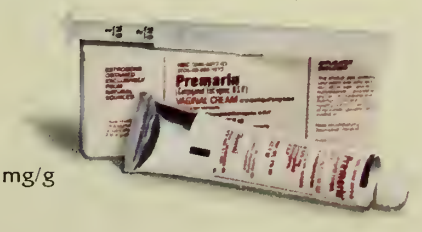
PREMARIN RESTORES THE VAGINAL ENVIRONMENT

In the postmenopausal woman, decreasing levels of estrogen can have devastating effects on a woman's sexual functioning. The pH of vaginal secretions rises, promoting the growth of contaminating organisms. The vaginal epithelium dries and thins, becoming susceptible to irritation, injury, and infection. Sexual relations may be difficult or impossible.

PREMARIN (Conjugated Estrogens, U.S.P.) Vaginal Cream focuses therapy at the site of the problem. Vaginal dryness is relieved, pH reverts to its normal acidity, and the epithelium thickens and becomes more resistant to injury and infection. With the vaginal environment returned to its premenopausal state, sexual function may improve.

PREMARIN®

(CONJUGATED ESTROGENS, U.S.P.) Vaginal Cream



0.625 mg/g

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Please see last page for brief summary of full prescribing information.

BRIEF SUMMARY *(FOR FULL PRESCRIBING INFORMATION AND PATIENT INFORMATION SEE PACKAGE CIRCULAR)*

PREMARIN® Brand of Conjugated Estrogens Tablets, U.S.P.

PREMARIN® Brand of Conjugated Estrogens, U.S.P. Vaginal Cream in a nonliquefying base

1 ESTROGENS HAVE BEEN REPORTED TO INCREASE THE RISK OF ENDOMETRIAL CARCINOMA

Three independent case control studies have reported an increased risk of endometrial cancer in postmenopausal women exposed to exogenous estrogens for more than one year. This risk was independent of the other known risk factors for endometrial cancer. These studies are further supported by the finding that incidence rates of endometrial cancer have increased sharply since 1969 in eight different areas of the United States with population based cancer reporting systems, an increase which may be related to the rapidly expanding use of estrogens during the last decade. The three case control studies reported that the risk of endometrial cancer in estrogen users was about 4.5 to 13.9 times greater than in nonusers. The risk appears to depend on both duration of treatment and on estrogen dose. In view of these findings, when estrogens are used for the treatment of menopausal symptoms, the lowest dose that will control symptoms should be utilized and medication should be discontinued as soon as possible. When prolonged treatment is medically indicated, the patient should be reassessed on at least a semiannual basis to determine the need for continued therapy. Although the evidence must be considered preliminary, one study suggests that cyclic administration of low doses of estrogen may carry less risk than continuous administration; it therefore appears prudent to utilize such a regimen. Close clinical surveillance of all women taking estrogens is important. In all cases of undiagnosed persistent or recurring abnormal vaginal bleeding, adequate diagnostic measures should be undertaken to rule out malignancy. There is no evidence at present that "natural" estrogens are more or less hazardous than "synthetic" estrogens at equiestrogenic doses.

2 ESTROGENS SHOULD NOT BE USED DURING PREGNANCY

The use of female sex hormones, both estrogens and progestogens, during early pregnancy may seriously damage the offspring. It has been shown that females exposed in utero to diethylstilbestrol, a non-steroidal estrogen, have an increased risk of developing in later life a form of vaginal or cervical cancer that is ordinarily extremely rare. This risk has been estimated as not greater than 4 per 1000 exposures. Furthermore, a high percentage of such exposed women (from 30 to 90 percent) have been found to have vaginal adenosis, epithelial changes of the vagina and cervix. Although these changes are histologically benign, it is not known whether they are precursors of malignancy. Although similar data are not available with the use of other estrogens, it cannot be presumed they would not induce similar changes. Several reports suggest an association between intrauterine exposure to female sex hormones and congenital anomalies, including congenital heart defects and limb reduction defects. One case control study estimated a 4.7-fold increased risk of limb reduction defects in infants exposed in utero to sex hormones (oral contraceptives, hormone withdrawal tests for pregnancy, or attempted treatment for threatened abortion). Some of these exposures were very short and involved only a few days of treatment. The data suggest that the risk of limb reduction defects in exposed fetuses is somewhat less than 1 per 1000. In the past, female sex hormones have been used during pregnancy in an attempt to treat threatened or habitual abortion. There is considerable evidence that estrogens are ineffective for these indications, and there is no evidence from well controlled studies that progestogens are effective for these uses. If PREMARIN is used during pregnancy, or if the patient becomes pregnant while taking this drug, she should be apprised of the potential risks to the fetus, and the advisability of pregnancy continuation.

DESCRIPTION: PREMARIN (Conjugated Estrogens, U.S.P.) contains a mixture of estrogens, obtained exclusively from natural sources, blended to represent the average composition of material derived from pregnant mares' urine. It contains estrone, equilin, and 17α-dihydroequilin, together with smaller amounts of 17α-estradiol, equilenin, and 17α-dihydroequilenin as salts of their sulfate esters.

INDICATIONS: Based on a review of PREMARIN Tablets by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications for use as follows:

Effective: 1. Moderate to severe vasomotor symptoms associated with the menopause. (There is no evidence that estrogens are effective for nervous symptoms or depression without associated vasomotor symptoms, and they should not be used to treat such conditions.)

2. Atrophic vaginitis.

3. Kraurosis vulvae.

4. Female hypogonadism.

5. Female castration.

6. Primary ovarian failure.

7. Breast cancer (for palliation only) in appropriately selected women and men with metastatic disease.

8. Prostatic carcinoma: palliative therapy of advanced disease.

9. Postpartum breast engorgement. Although estrogens have been widely used for the prevention of postpartum breast engorgement, controlled studies have demonstrated that the incidence of significant painful engorgement in patients not receiving such hormonal therapy is low and usually responsive to appropriate analgesic or other supportive therapy. Consequently, the benefit to be derived from estrogen therapy for this indication must be carefully weighed against the potential increased risk of puerperal thromboembolism associated with the use of large doses of estrogens.

PREMARIN HAS NOT BEEN SHOWN TO BE EFFECTIVE FOR ANY PURPOSE DURING PREGNANCY AND ITS USE MAY CAUSE SEVERE HARM TO THE FETUS (SEE BOXED WARNING).

"Probably" effective: For estrogen deficiency-induced osteoporosis, and only when used in conjunction with other important therapeutic measures such as diet, calcium, physiotherapy, and good general health-promoting measures. Final classification of this indication requires further investigation.

INDICATIONS: PREMARIN (Conjugated Estrogens, U.S.P.) Vaginal Cream is indicated in the treatment of atrophic vaginitis and kraurosis vulvae. PREMARIN Vaginal Cream HAS NOT BEEN SHOWN TO BE EFFECTIVE FOR ANY PURPOSE DURING PREGNANCY AND ITS USE MAY CAUSE SEVERE HARM TO THE FETUS (SEE BOXED WARNING).

CONTRAINDICATIONS: Estrogens should not be used in women (or men) with any of the following conditions: 1. Known or suspected cancer of the breast except in appropriately selected patients being treated for metastatic disease. 2. Known or suspected estrogen dependent neoplasia. 3. Known or suspected pregnancy (See Boxed Warning). 4. Undiagnosed abnormal genital bleeding. 5. Active thrombophlebitis or thromboembolic disorders. 6. A past history of thrombophlebitis, thrombosis, or thromboembolic disorders associated with previous estrogen use (except when used in treatment of breast or prostatic malignancy).

WARNINGS: Long term continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, cervix, vagina, and liver. There are now reports that estrogens increase the risk of carcinoma of the endometrium in humans. (See Boxed Warning.) At the present time there is no satisfactory evidence that estrogens given to postmenopausal women increase the risk of cancer of the breast, although a recent study has raised this possibility. There is a need for caution in prescribing estrogens for women with a strong family history of breast cancer or who have breast nodules, fibrocystic disease, or abnormal mammograms. A recent study has reported a 2- to 3-fold increase in the risk of surgically confirmed gallbladder disease in women receiving postmenopausal estrogens.

Adverse effects of oral contraceptives may be expected at the larger doses of estrogen used to treat prostatic or breast cancer or postpartum breast engorgement, it has been shown that there is an increased risk of thrombosis in men receiving estrogens for prostatic cancer and women for postpartum breast engorgement. Users of oral contraceptives have an increased risk of diseases, such as thrombophlebitis, pulmonary embolism, stroke, and myocardial infarction. Cases of retinal thrombosis, mesenteric thrombosis, and optic neuritis have been reported in oral contraceptive users. An increased risk of postsurgery thromboembolic complications has also been reported in users of oral contraceptives. If feasible, estrogen should be discontinued at least 4 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization. Estrogens should not be used in persons with active thrombophlebitis, thromboembolic disorders, or in persons with a history of such disorders in association with estrogen use. They should be used with caution in patients with cerebral vascular or coronary artery disease. Large doses (5 mg conjugated estrogens per day), comparable to those used to treat cancer of the prostate and breast have been shown to increase the risk of nonfatal myocardial infarction, pulmonary embolism and thrombophlebitis. When doses of this size are used, any of the thromboembolic and thrombotic adverse effects should be considered a clear risk.

Benign hepatic adenomas should be considered in estrogen users having abdominal pain and tenderness, abdominal mass, or hypovolemic shock. Hepatocellular carcinoma has been reported in women taking estrogen containing oral contraceptives. Increased blood pressure may occur with use of estrogens in the menopause and blood pressure should be monitored with estrogen use. A worsening of glucose tolerance has been observed in patients on estrogen-containing oral contraceptives. For this reason, diabetic patients should be carefully observed. Estrogens may lead to severe hypercalcemia in patients with breast cancer and bone metastases.

PRECAUTIONS: Physical examination and a complete medical and family history should be taken prior to the initiation of any estrogen therapy with special reference to blood pressure, breasts, abdomen, and pelvic organs, and should include a Papanicolau smear. As a general rule, estrogen should not be prescribed for longer than one year without another physical examination being performed. Conditions influenced by fluid retention such as asthma, epilepsy, migraine, and cardiac or renal dysfunction, require careful observation. Certain patients may develop manifestations of excessive estrogenic stimulation, such as abnormal or excessive uterine bleeding, mastodynia, etc. Prolonged administration of unopposed estrogen therapy has been reported to increase the risk of endometrial hyperplasia in some patients. Oral contraceptives appear to be associated with an increased incidence of mental depression. Patients with a history of depression should be carefully observed. Preexisting uterine leiomyomata may increase in size during estrogen use. The pathologist should be advised of estrogen therapy when relevant specimens are submitted. If jaundice develops in any patient receiving estrogen, the medication should be discontinued while the cause is investigated. Estrogens should be used with care in patients with impaired liver function, renal insufficiency, metabolic bone diseases associated with hypercalcemia, or in young patients in whom bone growth is not complete.

The following changes may be expected with larger doses of estrogen:

a. Increased sulfobromophthalein retention.

b. Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3; increased norepinephrine-induced platelet aggregability.

c. Increased thyroid binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by PBI, T4 by column, or T4 by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG; free T4 concentration is unaltered.

d. Impaired glucose tolerance.

e. Decreased pregnanediol excretion.

f. Reduced response to metyrapone test.

g. Reduced serum folate concentration.

h. Increased serum triglyceride and phospholipid concentration.

As a general principle, the administration of any drug to nursing mothers should be done only when clearly necessary since many drugs are excreted in human milk.

ADVERSE REACTIONS: The following have been reported with estrogenic therapy, including oral contraceptives: breakthrough bleeding, spotting, change in menstrual flow, dysmenorrhea, premenstrual-like syndrome; amenorrhea during and after treatment, increase in size of uterine fibromyomata, vaginal candidiasis, change in cervical erosion and in degree of cervical secretion; cystitis-like syndrome; tenderness, enlargement, secretion (of breasts); nausea, vomiting, abdominal cramps, bloating; cholestatic jaundice; chloasma or melasma which may persist when drug is discontinued; erythema multiforme; erythema nodosum; hemorrhagic eruption; loss of scalp hair; hirsutism; steepening of corneal curvature; intolerance to contact lenses; headache, migraine, dizziness; mental depression; chorea; increase or decrease in weight; reduced carbohydrate tolerance; aggravation of porphyria, edema; changes in libido.

ACUTE OVERDOSAGE: May cause nausea, and withdrawal bleeding may occur in females.

DOSAGE AND ADMINISTRATION:

PREMARIN® Brand of Conjugated Estrogens Tablets, U.S.P.

1. *Given cyclically for short-term use only.* For treatment of moderate to severe vasomotor symptoms, atrophic vaginitis, or kraurosis vulvae associated with the menopause (0.3 to 1.25 mg or more daily).

The lowest dose that will control symptoms should be chosen and medication should be discontinued as promptly as possible.

Administration should be cyclic (e.g., three weeks on and one week off).

Attempts to discontinue or taper medication should be made at three to six month intervals.

2. *Given cyclically.* Female hypogonadism. Female castration. Primary ovarian failure. Osteoporosis.

Female hypogonadism—2.5 to 7.5 mg daily, in divided doses for 20 days, followed by a rest period of 10 days' duration. If bleeding does not occur by the end of this period, the same dosage schedule is repeated. The number of courses of estrogen therapy necessary to produce bleeding may vary depending on the responsiveness of the endometrium.

If bleeding occurs before the end of the 10 day period, begin a 20 day estrogen-progestin cyclic regimen with PREMARIN (Conjugated Estrogens Tablets, U.S.P.), 2.5 to 7.5 mg daily in divided doses, for 20 days. During the last five days of estrogen therapy, give an oral progestin. If bleeding occurs before this regimen is concluded, therapy is discontinued and may be resumed on the fifth day of bleeding.

Female castration and primary ovarian failure—1.25 mg daily, cyclically. Adjust upward or downward according to response of the patient. For maintenance, adjust dosage to lowest level that will provide effective control.

Osteoporosis (to retard progression)—1.25 mg daily, cyclically.

3. *Given for a few days.* Prevention of postpartum breast engorgement—3.75 mg every four hours for five doses, or 1.25 mg every four hours for five days.

4. *Given chronically.* Inoperable progressing prostatic cancer—1.25 to 2.5 mg three times daily.

Inoperable progressing breast cancer in appropriately selected men and postmenopausal women—10 mg three times daily for a period of at least three months.

Patients with an intact uterus should be monitored for signs of endometrial cancer and appropriate measures taken to rule out malignancy in the event of persistent or recurring abnormal vaginal bleeding.

PREMARIN® Brand of Conjugated Estrogens, U.S.P. Vaginal Cream

Given cyclically for short-term use only. For treatment of atrophic vaginitis or kraurosis vulvae.

The lowest dose that will control symptoms should be chosen and medication should be discontinued as promptly as possible.

Administration should be cyclic (e.g., three weeks on and one week off).

Attempts to discontinue or taper medication should be made at three to six month intervals.

Usual dosage range: 2 to 4 g daily, intravaginally or topically, depending on the severity of the condition.

Treated patients with an intact uterus should be monitored closely for signs of endometrial cancer and appropriate diagnostic measures should be taken to rule out malignancy in the event of persistent or recurring abnormal vaginal bleeding.

HOW SUPPLIED: PREMARIN (Conjugated Estrogens Tablets, U.S.P.) No. 865: Each *purple* tablet contains 2.5 mg in bottles of 100 and 1,000. No. 866: Each *yellow* tablet contains 1.25 mg in bottles of 100 and 1,000. Also in Cycle Pack of 21 and in unit dose package of 100. No. 864: Each *white* tablet contains 0.9 mg in bottles of 100. Also in Cycle Pack of 21. No. 867: Each *maroon* tablet contains 0.625 mg in bottles of 100 and 1,000. Also in Cycle Pack of 21 and unit dose package of 100. No. 868: Each *green* tablet contains 0.3 mg in bottles of 100 and 1,000. The appearance of these tablets is a trademark of Ayerst Laboratories.

PREMARIN (Conjugated Estrogens, U.S.P.) Vaginal Cream: No. 872. Each gram contains 0.625 mg Conjugated Estrogens, U.S.P. (Also contains cetyl esters wax, cetyl alcohol, white wax, glyceryl monostearate, propylene glycol monostearate, methyl stearate, phenylethyl alcohol, sodium lauryl sulfate, glycerin, and mineral oil.)

Combination package: Each contains Net Wt. 1½ oz. (42.5 g) tube with one calibrated plastic applicator.

Also Available. Refill package: Each contains Net Wt. 1½ oz. (42.5 g) tube. **4340R1/285**

References: 1. Lindsay R, Hart DM, Clark DM: The minimum effective dose of estrogen for prevention of postmenopausal bone loss. *Obstet Gynecol* 1984;63:759-763. **2.** Katz WA: *Rheumatic Diseases: Diagnosis and Management*. Philadelphia, JB Lippincott Co, 1977, p 672. **3.** Reese WD: A better way to screen for osteoporosis. *Contemp Ob/Gyn* 1983;22(November):116-131. **4.** Judd HL: After the menopause. *Transition* 1983;1:19-30. **5.** Erlik Y, Tataryn IV, Meldrum DR, et al: Association of waking episodes with menopausal hot flushes. *JAMA* 1981;245:1741-1744. **6.** Meldrum DR: The pathophysiology of postmenopausal symptoms. *Sem Reprod Endocrinol* 1983;1(February):11-17.

Ayerst® AYERST LABORATORIES
New York, N.Y. 10017

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Upjohn

The Upjohn Company, Kalamazoo, Michigan 49001

Medrol® Dosepak™ Unit-of-Use

4 mg methylprednisolone tablets, USP

The explicit printed dosage instructions that accompany each *Dosepak* make it easy for the patient to understand and follow the dosage regimen.

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(Continued from Page 484)

May 31-June 1—**Internal Medicine Update.** Portland. Friday-Saturday. Marriott Hotel. Contact: OHSU-CME.

June 28—**Osteoporosis Conference.** Portland. Friday. Red Lion Lloyd Center. Contact: OHSU-CME.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah State Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. They also must meet the definition of Utah Approved CME Credit for the purpose of medical license reregistration in Utah. Accredited institutions wishing to list AMA Category 1/Utah Approved CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, Utah 84102; or phone (801) 355-5290. For information on CME accreditation or on the CME requirements of the Utah Physicians' Licensing Board, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution or the CME office for current details. .

MEDICAL GRAND ROUNDS

Each Wednesday—8:00-9:00 a.m. Alternating between University of Utah Medical Center and VA Medical Center, Salt Lake City. Contact: William D. Odell, MD, PhD, Professor and Chairman, Dept. of Internal Medicine, Univ. of Utah, (801) 581-7606.

* * *

June 7-8—**Advanced Trauma Life Support** (Sponsor: University of Utah). Friday-Saturday. Salt Lake Quality Inn, Salt Lake City. 16 hrs. $405. Contact: Kim Tanner, RN, (801) 533-6608.

July 14-19—**Summer Update in Clinical Microbiology and Immunology** (Sponsor: University of Utah). Sunday-Friday. Jackson Hole, American Snow King. 23 hrs. Contact: John Matsen, MD, (801) 581-7480.

SPONSORS OF COURSES—ABBREVIATIONS

AF: Arthritis Foundation, 1174 East 2700 South, Salt Lake City 84117. (801) 466-9389.

CH: Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price, UT 84501. (801) 637-4800.

CWH: Cottonwood Hospital, 5770 South 300 East, Salt Lake City 84101. (801) 262-3461.

FHP: Family Health Program/Utah, 323 South Sixth East, Salt Lake City 84102. (801) 335-1234. Contact: Kay Schultz for course information.

HAFB: Hill Air Force Hospital, Hill Air Force Base 84406. (801) 777-1262.

HCH: Holy Cross Hospital, 1045 East First South, Salt Lake City 84102. (801) 350-4744.

LDSH: Latter-Day Saints Hospital, 325 8th Avenue, Salt Lake City 84143. (801) 350-1100.

MDH: McKay-Dee Hospital Center, 3939 Harrison Blvd., Ogden 84409. (801) 399-4141.

OEH: Rocky Mountain Center for Occupational and Environmental Health, 50 North Medical Drive, Salt Lake City 84132. (801) 581-8719.

OSS: Ogden Surgical Society, PO Box 9311, Ogden 84409.

PCMC: Primary Children's Medical Center, 320 12th Ave., Salt Lake City 84103. (801) 363-1221.

SHCC: Shriners Hospital for Crippled Children, Intermountain Unit, Fairfax Ave. at Virginia St., Salt Lake City 84103. (801) 532-5307.

SLSC: Salt Lake Surgical Center, 617 East 3900 South, Salt Lake City 84117. (801) 261-3141.

UAFP: Utah Academy of Family Physicians, 1146 Westminster Ave., Salt Lake City 84105. (801) 466-9478.

UUMC: University of Utah Medical Center, 50 North Medical Drive, Salt Lake City 84132. (801) 581-2258.

USMA: Utah State Medical Association, 540 East Fifth South, Salt Lake City 84102. (801) 355-7477.

UVH: Utah Valley Hospital, 1034 North Fifth West, Provo 84601. (801) 373-7850.

VAMC: Veterans Administration Medical Center, 500 Foothill Drive, Salt Lake City 84148. (801) 582-1565.

WASHINGTON

This listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121; or phone (206) 623-4801.

Brochures and Registration Forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

April 16—**Alzheimer's Disease.** Seattle. Tuesday. Ballard Hospital. Contact: U/W.

April 17-19—(MONTANA) **Internal Medicine Review.** Great Falls, Billings, Missoula. Wednesday-Friday. Contact: U/W.

April 18-20—**Death Investigation.** Seattle. Thursday-Saturday. Westin. Contact: U/W.

April 19—**Riverton Hospital Lectures.** Seattle. Friday. Riverton Hospital. Contact: U/W.

(Continued on Page 493)

COURSE SPONSORS AND CONTACT INFORMATION

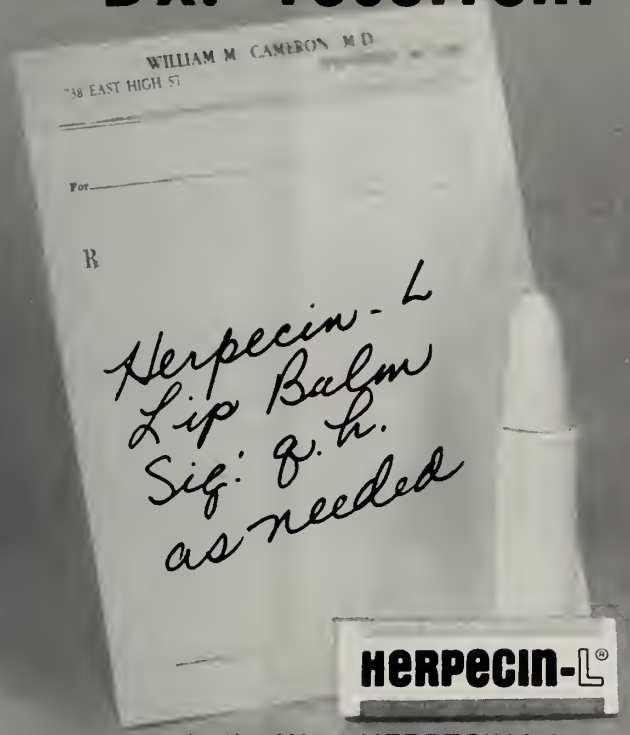
CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

CME PIERCE COUNTY—Contact: Mrs Maxine Bailey, Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 223-6898.

Dx: recurrent herpes labialis



"HERPECIN-L is my **treatment of choice** for perioral herpes." GP, NY

"HERPECIN-L appears to actually **prevent** the blisters . . . used **soon enough.**" DDS, MN

"HERPECIN-L®. . . a **conservative approach** with **low risk/high benefits.**" MD, FL

"Used at **prodromal symptoms** . . . blisters **never formed** . . . remarkable." DH, MA

"(In clinical trials) . . . **response** was **dramatic. HERPECIN-L** . . proven **far superior.**" DDS, PA

"All patients claimed **shorter duration** . . . at **prodromal symptoms** . . . HERPECIN-L **averted** the attacks." MD, AK

OTC. *See P.D.R.* for information. For samples to make your own clinical evaluation, write: CAMPBELL LABORATORIES, INC., P.O. BOX 812WJMFDR STATION, NEW YORK, N.Y. 10150

In the West HERPECIN-L is available at all *Drug King, Fred Meyer, PayLess, Revco, Sav-On, SupeRx, Thrifty Drug Stores* and other select pharmacies.

CONTINUING MEDICAL EDUCATION

(Continued from Page 492)

April 20—**Flexible Sigmoidoscopy.** Bellevue. Saturday. Overlake Hospital Medical Center. 8 hrs. Cat I. $100. Contact: Nancy Aziz, Cont. Med. Ed., Overlake Hospital Medical Center, 1035 116th Ave. NE, Bellevue 98004. (206) 454-4011, ext. 2630.

April 22-May 3—**Rehab Medicine Review.** Seattle. 12 days. Seattle Sheraton. Contact: U/W.

April 23—**Sexually Transmitted Diseases.** Auburn. Tuesday. Auburn General Hospital. Contact: U/W.

April 26—**Riverton Hospital Lectures.** Seattle. Friday. Riverton Hospital. Contact: U/W.

April 26-27—**Sexual Assault.** Seattle. Friday-Saturday. Westin Hotel. Contact: U/W.

May 3—**Riverton Hospital Lectures.** Seattle. Friday. Riverton Hospital. Contact: U/W.

May 3-4—**Pharmacology Update.** Seattle. Friday-Saturday. Contact: VMMC.

May 9-10—**Issues in General Pediatrics.** Seattle. Thursday-Friday. Children's Orthopedic Hospital. Contact: U/W.

May 10—**Riverton Hospital Lectures.** Seattle. Friday. Riverton Hospital. Contact: U/W.

May 17—**Riverton Hospital Lectures.** Seattle. Friday. Riverton Hospital. Contact: U/W.

May 18—**Microcomputers in Rehab Medicine.** Seattle. Saturday. Contact: U/W.

May 21—**Using Pulmonary Function Tests.** Seattle. Tuesday. Ballard Hospital. Contact: U/W.

May 22-24—(MONTANA) **Internal Medicine Review.** Great Falls, Billings, Missoula. Wednesday-Friday. Contact: U/W.

May 28—**Travel and Illness.** Auburn. Tuesday. Auburn General Hospital. Contact: U/W.

May 30-31—**Controversies in Cardiovascular Issues.** Seattle. Thursday-Friday. Contact: U/W.

May 30-31—**Mental Health Policy Forum.** Seattle. Thursday-Friday. Westin. Contact: U/W.

May 31—**Riverton Hospital Lectures.** Seattle. Friday. Riverton Hospital. Contact: U/W.

June 6-7—**Behavioral Medicine.** Seattle. Thursday-Friday. Westin. Contact: U/W.

(Continued on Page 497)

"When it comes to cardiovascular medicine, I like to know exactly what my patients are swallowing."

There are doctors who say that generic drugs have a place in their practice—but not necessarily in the treatment of serious or potentially life-threatening disease. And when they consider that the average patient pays only about 45¢ a day for INDERAL (propranolol HCl) Tablets, there's not much left to discuss.

When it's INDERAL Tablets you want for the treatment of hypertension, angina, arrhythmias, or post-MI patients, make sure you specify "Dispense As Written" (DAW), "Do Not Substitute," or whatever is required in your State. That way, you'll know exactly what your patients will get.

Please see next page for brief summary of prescribing information.

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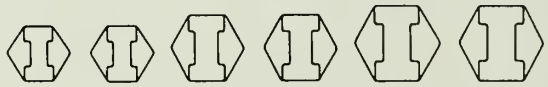

10 mg 20 mg 40 mg 60 mg 80 mg 90 mg*

BRIEF SUMMARY (FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE CIRCULAR.)

INDERAL® (propranolol hydrochloride) Tablets

CONTRAINDICATIONS

INDERAL is contraindicated in 1) cardiogenic shock, 2) sinus bradycardia and greater than first degree block, 3) bronchial asthma, 4) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL.

WARNINGS

CARDIAC FAILURE. Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta blockade may precipitate more severe failure. Although beta blockers should be avoided in overt congestive heart failure, if necessary they can be used with close follow-up in patients with a history of failure who are well compensated and are receiving digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle.

IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta blockers can, in some cases, lead to cardiac failure. Therefore, at the first sign or symptom of heart failure, the patient should be digitalized and/or treated with diuretics, and the response observed closely; or INDERAL should be discontinued (gradually, if possible).

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following abrupt discontinuance of INDERAL therapy. Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced over at least a few weeks and the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)—PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

MAJOR SURGERY. The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

INDERAL, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in starting and maintaining the heartbeat has also been reported with beta blockers.

DIABETES AND HYPOGLYCEMIA. Beta-adrenergic blockade may prevent the appearance of certain premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia in labile insulin-dependent diabetes. In these patients, it may be more difficult to adjust the dosage of insulin.

THYROTOXICOSIS. Beta blockade may mask certain clinical signs of hyperthyroidism. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

PRECAUTIONS

General. Propranolol should be used with caution in patients with impaired hepatic or renal function. INDERAL is not indicated for the treatment of hypertensive emergencies.

Beta-adrenoreceptor blockade can cause reduction of intraocular pressure. Patients should be told that INDERAL (propranolol hydrochloride) may interfere with the glaucoma screening test. Withdrawal may lead to a return of increased intraocular pressure.

Clinical Laboratory Tests. Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

DRUG INTERACTIONS. Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if INDERAL is administered. The added catecholamine-blocking action may produce an excessive reduction of resting sympathetic nervous activity which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility. Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In 18-month studies in both rats and mice, employing doses up to 150 mg/kg/day, there was no evidence of significant drug-induced toxicity. There were no drug-related tumorigenic effects at any of the dosage levels. Reproductive studies in animals did not show any impairment of fertility that was attributable to the drug.

Pregnancy. Pregnancy Category C. INDERAL has been shown to be embryotoxic in animal studies at doses about 10 times greater than the maximum recommended human dose.

There are no adequate and well-controlled studies in pregnant women. INDERAL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. INDERAL is excreted in human milk. Caution should be exercised when INDERAL is administered to a nursing woman.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Most adverse effects have been mild and transient and have rarely required the withdrawal of therapy.

Cardiovascular: bradycardia, congestive heart failure; intensification of AV block, hypotension; paresthesia of hands, thrombocytopenic purpura, arterial insufficiency, usually of the Raynaud type.

Central Nervous System: Lightheadedness, mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia, visual disturbances, hallucinations, an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Gastrointestinal: nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis.

Allergic: pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Respiratory: bronchospasm.

Hematologic: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Auto-Immune: In extremely rare instances, systemic lupus erythematosus has been reported.

Miscellaneous: alopecia. LE-like reactions, psoriasiform rashes, dry eyes, male impotence, and Peyronie's disease have been reported rarely. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been associated with propranolol.

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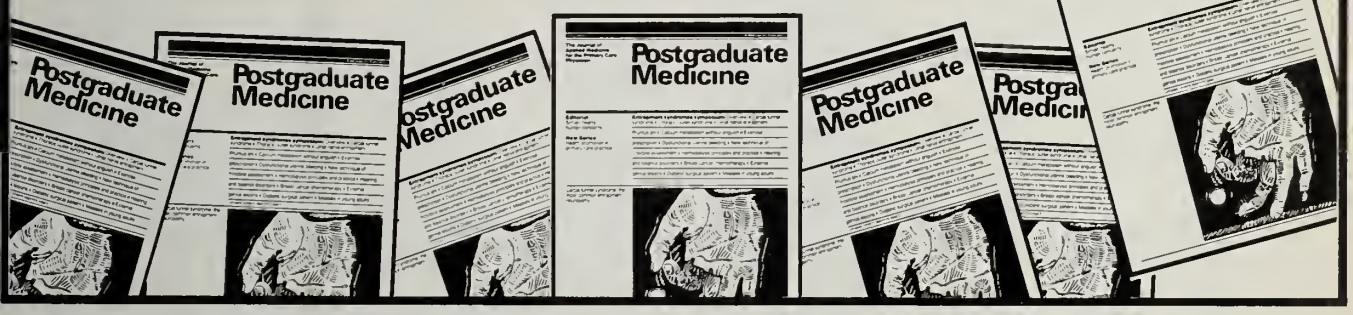

CONTINUING MEDICAL EDUCATION

(Continued from Page 493)

June 6-8—**Medical Emergencies.** Seattle. Thursday-Saturday. Contact: VMMC.

June 7—**Riverton Hospital Lectures.** Seattle. Friday. Riverton Hospital. Contact: U/W.

June 13-14—**Ischemic Heart Disease.** Seattle. Thursday-Friday. Westin. Contact: U/W.

June 13-14—**Advances in Internal Medicine.** Seattle. Thursday-Friday. U/W HUB. Contact: U/W.

June 14—**Riverton Hospital Lectures.** Seattle. Friday. Riverton Hospital. Contact: U/W.

June 15—**Contemporary Thoracic Imaging.** Seattle. Saturday. U/W South Campus Center. Contact: U/W.

June 18—**Small Computers in Medicine.** Seattle. Tuesday. Ballard Hospital. Contact: U/W.

June 19-20—**Financial Planning for Physicians.** Victoria, BC. Wednesday-Friday. Empress Hotel. Contact: U/W.

June 21—**Riverton Hospital Lectures.** Seattle. Friday. Riverton Hospital. Contact: U/W.

June 21-22—**Nutrition of Hospitalized Patient.** Vancouver, BC. Saturday-Sunday. Contact: U/W.

June 25—**What's New in Antibiotics.** Auburn. Tuesday. Auburn General Hospital. Contact: U/W.

June 26-29—**(OREGON) Washington State Chapter, American College of Surgeons.** Sun River, Oregon. Wednesday-Saturday. Sun River Resort. Contact: Richard P. Billingham, MD, 801 Broadway, Suite 712, Seattle 98122. (206) 624-2107.

June 28—**Riverton Hospital Lectures.** Seattle. Friday. Riverton Hospital. Contact: U/W.

July 8-10—**Scientific Aspects of Dance/Exercising Women.** Seattle. Monday-Wednesday. Westin. Contact: U/W.

WYOMING

June 23-26—**Wyoming Medical Society—Annual Meeting.** Jackson Lake Lodge, Moran. Sunday-Wednesday. Contact: WMS, PO Drawer 4009, Cheyenne 82003-4009. ◆

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For the Majority of Patient Types Over 50 ▪ Black ▪ Physically Active ▪ Asthmatic

*Not for initial therapy. See brief summary.

Serum K^+ and BUN should be checked periodically (see Warnings and Precautions).

Before prescribing, see complete prescribing information in SK&F CO. literature or *PDR*. The following is a brief summary.

WARNING

This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Contraindications: Concomitant use with other potassium-sparing agents such as spironolactone or amiloride. Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: **Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired.** If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics.

Precautions: The bioavailability of the hydrochlorothiazide component of 'Dyazide' is about 50% of the bioavailability of the single entity. Theoretically, a patient transferred from the single entities of Dyrenium (triamterene, SK&F CO.) and hydrochlorothiazide may show an increase in blood pressure or fluid retention. Similarly, it is also possible that the lesser hydrochlorothiazide bioavailability could lead to increased serum potassium levels. However, extensive clinical experience with 'Dyazide' suggests that these conditions have not been commonly observed in clinical practice. Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids, and during concurrent use with amphotericin B or corticosteroids or corticotropin [ACTH]). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Cumulative effects of the drug may develop in patients with impaired renal function. Thiazides should be used with caution in patients with impaired hepatic function. They can precipitate coma in patients with severe liver disease. Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic and hemolytic anemia have been reported with thiazides. Thiazides may cause manifestation of latent diabetes mellitus. The effects of oral anticoagulants may be decreased when used concurrently with hydrochlorothiazide; dosage adjustments may be necessary. Clinically insignificant reductions in arterial responsiveness to norepinephrine have been reported. Thiazides have also been shown to increase the paralyzing effect of nondepolarizing muscle relaxants such as tubocurarine. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. Triamterene has been found in renal stones in association with the other usual calculus components. Therefore, 'Dyazide' should be used with caution in patients with histories of stone formation. A few occurrences of acute renal failure have been reported in patients on 'Dyazide' when treated with indomethacin. Therefore, caution is advised in administering nonsteroidal anti-inflammatory agents with 'Dyazide'. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine. Hypokalemia is uncommon with 'Dyazide', but should it develop, corrective measures should be taken such as potassium supplementation or increased dietary intake of potassium-rich foods. Corrective measures should be instituted cautiously and serum potassium levels determined. Discontinue corrective measures and 'Dyazide' should laboratory values reveal elevated serum potassium. Chloride deficit may occur as well as dilutional hyponatremia. Concurrent use with chlorpropamide may increase the risk of severe hyponatremia. Serum PBI levels may decrease without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. 'Dyazide' should be withdrawn before conducting tests for parathyroid function.

Thiazides may add to or potentiate the action of other antihypertensive drugs.

Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances; postural hypotension (may be aggravated by alcohol, barbiturates, or narcotics). Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and respiratory distress including pneumonitis and pulmonary edema, transient blurred vision, sialadenitis, and vertigo have occurred with thiazides alone. Triamterene has been found in renal stones in association with other usual calculus components. Rare incidents of acute interstitial nephritis have been reported. Impotence has been reported in a few patients on 'Dyazide', although a causal relationship has not been established.

Supplied: **'Dyazide' is supplied as a red and white capsule, in bottles of 1000 capsules; Single Unit Packages (unit-dose) of 100 (intended for institutional use only); in Patient-Pak™ unit-of-use bottles of 100.**

BRS-DZ:L39

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The unique red and white Dyazide® capsule: Your assurance of SK&F quality.

Clinical Investigation

Evaluation of Impotence in Older Men

SUSAN STANIK DAVIS, MD; SHARON P. VIOSCA; MORDECHAI GURALNIK; CLARA WINDSOR, MS; MATTHEW W. BUTTIGLIERI, PhD; J. DENNIS BAKER, MD; ARUN J. MEHTA, MD, *and* STANLEY G. KORENMAN, MD, *Sepulveda, California*

Careful evaluation was carried out in 93 men older than 50 with erectile dysfunction. Their mean age was 61 years and the disorder had been present for a mean of 4.5 years. While 14 men (15%) had psychosocial factors that may have been pertinent, only 2 scored poorly on an Affect Balance Scale and 3 were receiving psychoactive medications. Results of nocturnal penile tumescence were abnormal in 91%. In 39% penile-brachial pressure indices were suggestive of pelvic vascular disease and in 9% were consistent with a pelvic "steal syndrome." Pelvic or peripheral nerve conduction disorders were also commonly seen in 54%. Endocrinopathy may have contributed to the dysfunction in 35%. Twenty-one men had diabetes mellitus, two new cases of hypothyroidism were discovered and hypogonadism was diagnosed definitely in four and considered likely in five others. Coexisting medical conditions were found in more than 90% of the men, especially hypertension, use of antihypertensive medications and atherosclerotic disease. Previous prostatectomies (19%) and vasectomies (30%) were common in the surgical histories.

Given the wide range of disorders uncovered in older men complaining of impotence, diagnostic study of potential causes may lead to a more rational approach for the evaluation and management of these men.

(Davis SS, Viosca SP, Guralnik M, et al: Evaluation of impotence in older men [Clinical Investigation]. West J Med 1985 Apr; 142:499-505)

Contemporary emphasis on fitness and quality of life has led to increased expectations regarding sexual performance among aging couples. Despite a wide variation among persons, a pronounced decline in male sexual activity with age has been shown to occur.[1-5] While Kinsey's initial observations that erectile dysfunction increased from 28% at age 60 to about 50% by age 75 were made long ago,[1] only now are large numbers of older men seeking medical evaluation and treatment for impotence. In a recent survey of impotence among US veterans presenting at another Veterans Administration hospital, Slag and co-workers found a prevalence of 34% among men with a mean age of 62 years, and more than half of these said they would be interested in further investigation of their problem.[6]

Professional interest in sexual dysfunction broadened as it was realized that older men might have organic disorders as the major cause of impotence.[6-10] A high incidence of therapeutic drug use, vascular and neurologic disease and diabetes was found in sexually dysfunctional older men. Testosterone levels were usually in the normal range but some low values were seen. Thus, the traditional position that impotence is usually psychogenic[11] was not tenable in these men.

It was the objective of this study to comprehensively evaluate the factors that may contribute to the relatively common complaint of impotence in middle-aged and elderly men and to analyze the relation between reproductive hormonal measurements and the other underlying organic problems.

Subjects and Methods

Ninety-three veterans older than 50 were evaluated in the Sexual Dysfunction Clinic. The men were self-referred or sent by their primary physicians for evaluation and met the criteria of age over 50 years and no known alcoholism, uremia or advanced carcinoma. They had no previous diag-

From the Departments of Medicine (Drs Davis, Viosca, Guralnik, Windsor, Mehta and Korenman), Psychiatry (Dr Buttiglieri) and Surgery (Dr Baker), UCLA-San Fernando Valley Program and Veterans Administration Medical Center, Sepulveda, California.

Submitted, revised, December 17, 1984.

Reprint requests to Stanley G. Korenman, MD, Department of Medicine (111), VA Medical Center, 16111 Plummer Street, Sepulveda, CA 91343.

ABBREVIATIONS USED IN TEXT

NPT = nocturnal penile tumescence
SHBG = sex hormone-binding globulin
SD = standard deviation

nosis of Klinefelter's syndrome or other hypogonadal state. They all suffered erectile dysfunction—that is, failure to obtain and maintain adequate penile erection for intromission and coital orgasm.

The subjects were questioned about the characteristics of their sexual problem, their medical and surgical histories and all alcohol, medications or recreational drugs used. The time and rate of onset of the impotence, presence of morning erections, masturbatory function, uniformity versus selectivity of the disturbance, patient's and partner's attitude toward the problem, level of libido, quality of life-style, sexual relationships and subject's mood were assessed in interview and by using the Derogatis Sexual Function Inventory.[12] The ease of attaining, firmness and duration of erections, as well as the quantity of ejaculate and quality of orgasm, were elicited to determine the nature of the sexual dysfunction. Physical examination and general laboratory tests were carried out, including fasting glucose studies and tests of liver, renal and thyroid function.

Reproductive endocrine evaluation included blood sampling on three separate mornings (between 8 and 10 AM) for the measurement of testosterone, estradiol, estrone, luteinizing hormone, follicle-stimulating hormone by radioimmunoassay,[13] prolactin determined by radioimmunoassay technique with a rabbit antiserum to purified human pituitary prolactin (supplied by Radioassay Systems Laboratories, Inc), sex hormone-binding globulin (SHBG) capacity by dihydrotestosterone saturation and precipitation by ammonium sulfate modified from Rosner,[14] calculation of free testosterone by equilibrium dialysis[15] and free estradiol, utilizing precipitation of SHBG at 50% ammonium sulfate.[16]

Objective documentation of erectile function was obtained utilizing nocturnal penile tumescence (NPT) recording, of systolic pressure in the penile arteries by Doppler measurements and of pelvic and peripheral nerve function by electromyographic recording. While resources were available 11 subjects were admitted for two to three nights and NPT was monitored by electroencephalograph with a penile mercury strain gauge around the penile base and tip (registering both circumference change and duration of events) to observe whether they attained episodes of full penile tumescence normally seen during sleep.[17] They were awakened during the best tumescent event for assessment by the patient and a trained observer of rigidity and adequacy for vaginal penetration. Fifty-nine subjects used a Dacomed Snap-Gauge at home for two to four nights, which offers a measure of stiffness as well as circumference change. The snap-gauge placed around the shaft of the penis consisted of three plastic filaments with different release-force constants chosen to represent intracavernosal pressures achieved during erection.The filaments remained unbroken (indicating no or minimal erection), or up to all three could be broken (signifying that an erection occurred, likely to be of sufficient rigidity for intromission).[18]

Impaired blood flow to arteries of the penis was indicated by decreased systolic pressure in the penile arteries compared with the brachial artery pressure, expressed as a ratio, the penile-brachial index. A digital blood pressure cuff was placed around the base of the penis and systolic pressure recorded by Doppler technique. An index of less than 0.75 may be associated with bilateral aortoilial occlusions on angiographic studies and is "suggestive" of a vascular factor contributing to erectile dysfunction, while 0.6 or less is highly correlated with angiographic lesions and has been called "diagnostic" of vasculogenic impotence.[19] Men with such impaired vascular function rarely reported any sexual activity. The index was repeated after treadmill exercise in 54 of the men with no recent history of angina or myocardial infarction, since it is believed that some men with pelvic vascular disease may experience an external iliac "steal syndrome" (with early loss of erection after the onset of coital thrusting) yet have normal indices at rest.[20,21] A drop of at least 0.15 in the penile-brachial index after exercise was used to detect this loss of flow from the penile to gluteal and femoral regions.

The bulbocavernosus reflex latency time (recorded by the electromyographic response in the bulbocavernosus muscle after electrical stimulation by a ring electrode around the glans) was measured to test the reflex arc through the pudendal nerve and sacral erection center. The normal latency time is <42.5 ms.[22] Peripheral nerve sensory latencies and motor conduction velocities were also done.

Results

The results of the interview characterized the veterans and their sexual problems. The initial 93 men evaluated ranged in age from 50 to 80 years old with a mean (and median) of 61 ± 6 SD (standard deviation) years. Of the men, 91% had a steady sexual partner. A sexual problem had been apparent from four months to 20 years before presentation, with a mean of 4.5 ± 4 years. All described normal previous sexual function. At presentation, 42 men (45%) reported the inability to obtain any degree of erection under any circumstance; 47 (51%) had difficulty obtaining erections and achieved only weak, partial erections inadequate for vaginal intromission; 4 (4%) described the problem as rapidly losing a firm erection (premature erectile loss). Most subjects retained the ability to ejaculate without an erection.

The Derogatis Sexual Functioning Inventory is a self-report psychological inventory that contains ten subsets designed to measure several dimensions of sexual functioning. The subjects of this study were considerably older, of different social backgrounds and had more medical disease than the group on which the inventory was standardized. They scored below the thirtieth percentile on the nine distinct subtests: Information (below the thirtieth percentile), indicating less understanding of fundamental facts of anatomy, physiology and general hygiene regarding sexual functions; Experience (below the twentieth percentile), indicating constriction of sexual behavior and variety of sexual experiences; Drive (below the thirtieth percentile), indicating reduced level of interest or investment in sexual matters; Attitudes (fifteenth percentile), indicating more inhibitions, negative emotions and reduced communications; Symptoms (below the fifteenth percentile), indicating numerous somatic symptoms and high intensity of distress; Role (below seventh percentile), indicating imbalance of sex role characteristic in

the direction of hypermasculinity; Fantasy (twentieth percentile), indicating constriction in the variety of sexual fantasies; Body (below the tenth percentile), indicating dissatisfaction with own physical attractiveness and body image, and Satisfaction (below the thirtieth percentile), indicating a low degree of sexual satisfaction.

The tenth measure "Affect" is often used as a separate psychometric instrument, the Affects Balance Scale[23] measuring the balance between positive affects (joy, contentment, vigor, affection) and negative affects (anxiety, depression, guilt, hostility). On this scale, the subjects' mean score was just below the fortieth percentile, indicating a tendency towards negative affects. Only two men, however, had scores that were two standard deviations or more below the mean, indicating severe imbalance toward negative emotions.

On the two global indices of sexual functioning, our sample as a group scored much lower than the norm group as follows: below the second percentile on the Sexual Functioning Index and at the twentieth percentile on the Global Sexual Satisfaction Index. The global scores indicate that our subjects had serious deficiencies across the board in all important aspects of sexual function as measured by a summation of all the subtests of the inventory (Sexual Function Index) and by the subjects' conscious evaluation (Global Sexual Satisfaction Index) of their current level of sexual functioning.

NPT monitoring was completed in 70 of the 93 men. Sixty-four of these 70 men (91%) registered no nocturnal erections that could be considered adequate for vaginal penetration by rigidity criteria (broken snap-gauge filaments or observation), suggesting an organic cause. Only six men broke all the snap-gauge filaments on at least one monitored night, indicating a firm erection probably sufficient for penetration but of undocumented duration. All of the men tested who reported absent erections under all circumstances had abnormal findings on NPT (30/30). Of the 47 men complaining of weak erections 32/37 studied had abnormal NPT results while 5 broke all the filaments of the gauges. Two of three complaining of firm but short-lasting erections had abnormal results on NPT. Thus in most cases the NPT monitoring confirmed the clinical history.

In all, 24% of those undergoing vascular testing (21 of 86 men) had resting penile-brachial pressure indices suggestive of aortoilial disease (<0.75 but >0.6) and an additional 13 (15%) had indices considered diagnostic of vasculogenic impotence (≤ 0.6) (Table 1). Of these 13 men, 8 had evidence of other atherosclerotic disease and 7 were diabetic. Disease of more distal vessels (such as the internal pudendal arteries, dorsal and deep penile and bulbourethral arteries) might not be detected by the resting penile index and impairment of the vastly increased flow to the cavernous bodies required during erection may occur without affecting resting measurements. Fifty-four men agreed to exercise on a treadmill and 8 of these had a fall in the index of ≥ 0.15 after exercise, consistent with the pelvic steal syndrome. Five of these men also gave a history of other atherosclerotic disease and three had diabetes.

The men were found to have a high incidence of nerve pathology, either pelvic or peripheral. Of 87 men who consented to neurologic studies, the bulbocavernosus reflex was absent in 13 men and the latency time was prolonged (>42.5 ms) in 3 others. Overall, 54% of the 87 men who underwent evaluation of the bulbocavernosus reflex latency time, peripheral nerve sensory latencies and motor conduction velocities had abnormal findings on conduction tests. Neuropathy was more prevalent among the diabetic men; 43% of the nondiabetic men and 90% of the diabetic men had abnormalities on the tests.

TABLE 1.—*Penile-Brachial Pressure Index in Subjects With Abnormal Results*

Patient Number	Supine		Postexercise	
	Right	Left	Right	Left
5	0.67	0.67	. . .	. . .
6	0.39	0.33	0.50	0.45
7	0.81	0.69	0.68	0.55
13	0.65	0.82	0.80	0.87
16	0.62	0.82	. . .	. . .
18	0.57	0.57	1.00	1.00
21	0.40	0.40	0.21	0.17
28	0.69	0.69	0.60	0.67
31	0.60	0.80	0.67	0.83
33	0.65	0.71	0.67	0.73
36	0.73	0.51	0.46	0.42
39	0.57	0.50	0.66	0.66
41	0.69	0.69	0.27	0.27
42	0.80	0.67	. . .	. . .
43	0.75	0.67	0.85	0.77
44	0.71	0.79	0.60	0.60
47	0.69	0.65	0.27	0.40
50	0.53	0.73	. . .	. . .
51	0.58	0.58	. . .	. . .
54	0.62	0.77	. . .	0.69
59	0.62	0.77	. . .	. . .
62	0.69	0.75	. . .	. . .
65	0.56	0.63	0.67	0.53
66	0.67	0.69	0.69	0.65
67	0.59	0.65	0.89	0.78
69	0.85	0.69	0.86	0.71
73	0.62	0.77	0.71	0.86
75	0.58	0.77	0.47	0.60
76	0.62	0.57	0.81	0.68
79	0.55	0.55	. . .	. . .
80	0.67	0.74	. . .	. . .
88	0.73	0.73	. . .	. . .
89	0.69	0.77	0.78	0.93
91	0.69	0.75	. . .	. . .

The most common endocrinopathy discovered by history or hormonal studies was diabetes mellitus. In this group of men, 21 patients had a history of diabetes mellitus. All had abnormal results on NPT. There were nonsignificant trends towards younger age (59.6 versus 61.9 years) and more obesity (mean percent of ideal body weight, 124% versus 117%) in the diabetic men. However, their incidence of atherosclerotic diseases by history and abnormalities on vascular and neurologic testing was no different from the nondiabetic men. There was also no difference in the hormonal values. The only difference was the more common finding of neurologic disease ($P<.001$). Two additional men were found to have hypothyroidism.

A tentative diagnosis of hypogonadism, as defined by a mean testosterone value more than 2 SD below the mean of healthy adult men of all ages, was made in four men (Table 2). None of these four had gonadotropin elevation. Three had

TABLE 2.—*Endocrine Data*

Patient #	Age yrs	IBW %	T ng/dl	FT ng/dl	E_1 pg/ml	E_2 pg/ml	FE_2 pg/ml	LH mIU/ml	FSH mIU/ml	PRL mIU/ml
1 . . .	56	116	82	1.5	32	17	5.7	6.8	4.7	46.0
2 . . .	66	135	121	2.4	49	22	8.0	10.4	31.0	370.0
3 . . .	63	115	232	10.1	52	22	14.0	8.8	7.6	55.0
4 . . .	63	161	245	12.9	43	33	23.4	8.5	8.9	9.2
5 . . .	71	117	254	7.8	51	40	26.2	15.0	11.1	11.0
6 . . .	60	100	258	8.9	48	31	15.5	7.6	10.2	7.1
7 . . .	69	127	259	6.5	52	36	15.9	14.9	10.0	7.0
8 . . .	71	117	260	8.3	48	84	30.5	10.5	12.0	7.8
9 . . .	59	103	273	8.5	49	38	24.8	7.1	3.7	5.5
10 . . .	64	136	278	8.7	53	37	23.2	27.0	60.1	9.9
11 . . .	62	122	295	14.4	52	33	19.0	9.6	13.2	8.6
12 . . .	62	131	299	9.6	68	33	16.6	8.2	4.5	8.0
13 . . .	63	146	306	12.6	71	57	32.9	8.3	12.3	5.9
14 . . .	66	139	308	9.1	34	34	15.0	10.0	18.5	7.8
15 . . .	52	144	313	12.1	36	51	31.9	6.9	6.8	10.3
16 . . .	54	100	314	3.6	33	34	9.5	26.0	124.0	7.2
17 . . .	64	108	315	10.8	68	36	22.8	11.4	6.7	5.5
18 . . .	61	140	317	12.2	44	49	31.5	18.3	32.5	9.7
19 . . .	64	135	320	9.7	90	68	36.9	7.2	10.5	7.0
20 . . .	70	114	340	7.9	53	36	14.9	12.4	17.0	8.8
21 . . .	63	115	354	12.2	44	23	12.7	11.5	13.3	10.8
22 . . .	65	102	361	9.6	48	26	14.3	9.3	7.5	6.8
23 . . .	61	114	365	10.5	72	48	22.4	9.8	7.8	12.8
24 . . .	50	133	370	12.4	53	26	13.5	10.5	2.6	8.3
25 . . .	61	132	376	10.3	83	41	20.7	6.3	3.5	9.0
26 . . .	54	114	380	15.4	31	38	21.8	8.5	10.8	13.9
27 . . .	57	147	386	12.0	50	48	24.6	7.3	10.8	7.1
28 . . .	63	136	391	9.3	60	34	13.9	9.2	10.2	32.5
29 . . .	64	131	392	10.6	58	49	24.8	9.4	5.4	12.7
30 . . .	60	109	400	17.3	46	22	14.3	13.3	15.7	18.4
31 . . .	62	108	400	13.7	37	59	31.6	4.9	3.6	5.9
32 . . .	69	105	412	10.5	54	24	13.3	5.2	4.1	6.7
33 . . .	68	145	418	14.2	40	41	27.0	15.5	18.6	9.7
34 . . .	64	147	418	8.0	48	56	24.7	6.3	7.1	11.6
35 . . .	71	132	418	11.1	66	80	49.6	18.0	18.0	11.6
36 . . .	50	135	420	12.3	183	92	36.0	10.5	5.2	14.0
37 . . .	56	137	425	12.1	30	44	25.5	5.0	5.4	9.8
38 . . .	65	108	426	11.9	83	62	35.3	6.3	7.1	4.8
39 . . .	66	125	429	15.2	57	62	36.6	12.2	9.4	7.0
40 . . .	60	115	433	11.8	59	32	13.5	16.7	26.7	18.5
41 . . .	62	117	435	11.0	53	21	13.3	20.0	5.7	8.9
42 . . .	66	124	445	12.9	64	42	14.8	8.7	5.3	6.0
43 . . .	61	117	450	13.3	34	39	23.1	9.1	10.2	8.7
44 . . .	56	104	450	13.7	30	28	18.2	13.5	8.6	2.9
45 . . .	72	135	452	10.5	43	43	17.6	12.4	6.8	13.8
46 . . .	69	124	460	12.7	78	31	13.1	9.3	12.3	13.6
47 . . .	55	115	468	9.2	36	36	15.8	10.1	4.7	4.5
48 . . .	55	122	480	18.9	40	53	30.7	7.4	5.6	18.9
49 . . .	58	126	490	12.6	46	34	15.3	7.2	8.0	11.1
50 . . .	55	139	496	10.9	42	33	14.4	7.8	25.2	10.3
51 . . .	56	89	500	8.1	57	14	3.4	9.8	14.4	7.1
52 . . .	67	116	520	11.9	44	30	10.4	13.3	11.8	7.3
53 . . .	67	112	525	13.5	36	26	11.0	12.4	18.8	22.8
54 . . .	65	109	547	12.6	42	40	20.6	12.2	2.0	7.8
55 . . .	55	114	550	12.1	55	36	13.4	10.3	37.7	7.6
56 . . .	58	102	555	17.1	80	110	56.4	5.6	6.1	7.1
57 . . .	72	104	555	11.1	50	45	23.0	10.2	9.9	8.4
58 . . .	53	123	560	16.7	48	54	27.5	9.8	5.5	5.7
59 . . .	59	115	560	12.8	58	57	27.2	7.0	4.5	13.7
60 . . .	66	120	575	16.7	45	56	38.3	8.3	7.6	9.3
61 . . .	80	104	585	12.0	52	33	10.0	12.0	16.0	6.4
62 . . .	58	117	586	15.0	59	59	34.4	19.9	9.3	8.7
63 . . .	56	115	587	14.1	31	62	34.5	24.5	18.0	9.3
64 . . .	67	94	590	11.6	34	26	8.7	8.1	5.9	12.0
65 . . .	57	108	593	24.9	54	15	8.9	15.2	26.8	7.2
66 . . .	60	123	600	13.7	111	58	26.8	9.5	9.0	7.3
67 . . .	67	106	615	9.6	31	38	12.7	7.3	3.5	5.2
68 . . .	64	120	630	15.5	56	27	10.8	11.5	48.0	8.4
69 . . .	55	101	630	16.3	44	44	18.6	12.0	12.0	7.9
70 . . .	65	106	650	15.2	58	27	9.9	11.5	10.7	12.0
71 . . .	57	133	653	15.9	40	65	28.1	21.0	44.2	11.9
72 . . .	65	101	656	14.5	70	39	21.3	16.0	10.0	5.6
73 . . .	56	131	665	23.9	56	60	39.3	8.3	8.1	13.2
74 . . .	57	102	690	23.1	112	37	22.7	6.0	13.2	14.3
75 . . .	53	100	695	15.6	80	43	15.8	19.0	25.5	5.8
76 . . .	53	124	700	26.3	55	54	37.3	12.8	14.5	8.8
77 . . .	68	112	705	10.5	61	66	20.0	8.3	9.1	8.9
78 . . .	63	139	720	19.3	85	97	29.3	12.5	20.7	13.5
79 . . .	63	101	730	8.4	44	35	8.4	10.3	12.1	5.8
80 . . .	71	105	737	12.8	53	25	9.0	8.7	7.1	15.6
81 . . .	61	104	740	14.3	55	54	18.0	15.3	20.5	10.4
82 . . .	54	97	744	20.0	62	51	25.1	6.1	9.4	8.5
83 . . .	55	132	750	18.2	30	36	15.1	10.0	11.5	6.1
84 . . .	62	117	760	18.6	113	125	58.8	13.2	13.6	14.5
85 . . .	50	95	770	16.1	49	45	17.2	8.7	3.0	24.8
86 . . .	55	105	780	23.0	64	40	23.7	9.5	14.5	7.4
87 . . .	61	108	790	19.0	53	33	19.8	5.2	5.1	5.7
88 . . .	55	106	792	14.4	48	54	27.3	6.8	6.4	4.8
89 . . .	52	111	807	21.4	67	43	23.4	12.5	26.0	9.4
90 . . .	61	121	810	19.7	51	40	21.0	9.3	8.8	9.5
91 . . .	62	109	857	13.4	53	53	24.4	6.4	5.2	3.1
92 . . .	63	94	923	19.5	62	68	33.4	12.9	13.3	6.8
93 . . .	63	127	960	26.2	126	112	60.1	15.0	23.5	13.4

IBW=ideal body weight T=testosterone FT=free thyroxine E_1=estrone E_2=estradiol FE_2=free estradiol LH=luteinizing hormone FSH=follicle stimulating hormone PRL=prolactin

hyperprolactinemia; one had a nonsecreting pituitary tumor, another a prolactinoma and the third idiopathic hyperprolactinemia. The fourth man was felt to be eugonadal with decreased testosterone levels due to obesity (161% of ideal body weight) reflected in decreased SHBG capacity, normal free thyroxine values, normal gonadotropins and prolactin. In all, 25 men had testosterone values between 250 and 400 ng per dl (more than 1 SD below the laboratory mean but not 2 SD below). Four of these men with borderline total testosterone levels had abnormal free thyroxine values (<8 ng per dl). One also had clearly elevated gonadotropin levels and the diagnosis was probable primary hypogonadism. The other three had luteinizing hormone levels at the upper limit of normal and, along with two additional patients with high luteinizing hormone levels and free thyroxine values at the lower limit of normal, were given a working diagnosis of primary hypogonadism. The question of secondary hypogonadism due to a central or pituitary lesion in the remaining 19 men with borderline testosterone and normal luteinizing hormone values could be raised and would be difficult to detect by static hormonal tests.

Normal testosterone and free thyroxine levels were noted in 64 men. While their mean gonadotropin levels were normal, 11 of these "eugonadal" subjects had luteinizing hormone elevations in the pooled serum. The lack of utility of baseline gonadotropin values as a measure of effect of the steroid at target tissues to improve the diagnostic criteria for hypogonadism in the older subjects with borderline or normal testosterone values is shown in Figure 1, where testosterone, free thyroxine and estradiol levels were plotted against luteinizing hormone and testosterone plotted against follicle-stimulating hormone for the entire group. No relationship between the steroid hormones and gonadotropins was seen.

The interrelationships between the various hormonal measurements were statistically evaluated. Even after excluding the three men with hyperprolactinemia, there was a paucity of hormonal interrelationships. The only significant correlations found were expected, positive between testosterone and free thyroxine ($r=0.7142$, $P<.001$), testosterone and estradiol ($r=0.320$, $P<.005$), free estradiol and ideal body weight ($r=0.2429$, $P<.02$) and estradiol and estrone ($r=0.5398$, $P<.001$). Additionally age was inversely correlated with free thyroxine ($r=-0.3353$, $P<.001$) and percent of ideal body weight was inversely correlated with testosterone ($r=-0.3774$, $P<.001$) and with the SHBG capacity ($r=-0.315$, $P<.005$), but not free thyroxine.

Recent reports suggesting a relationship between atherosclerotic heart disease and serum estrogen levels[24] and diabetes and estrogen elevation[25] led us to evaluate subsets with high (more than 2 SD above the mean of normal men, estradiol ≥50 pg per ml or estrone ≥60 pg per ml) versus low or normal (estradiol <50 pg per ml and estrone <60 pg per ml) estrogen groups. In this limited series there was no difference in the prevalence of coronary, cerebral or peripheral athero-

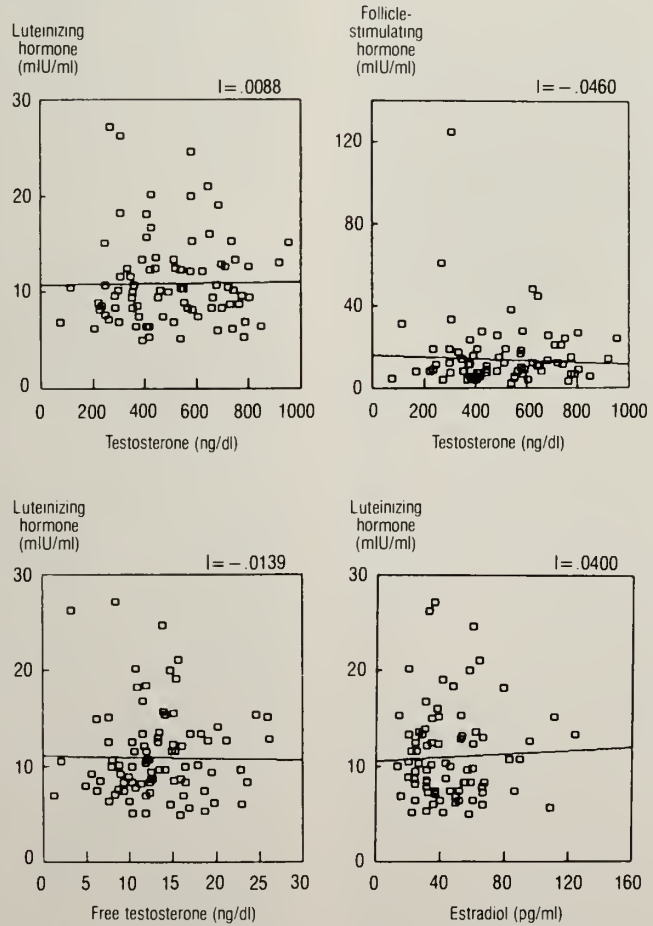

Figure 1.—Lack of relation between the steroid hormones and gonadotropins.

sclerosis or penile vascular insufficiency on Doppler examination among those older men with the higher estradiol values when compared by χ^2 tests with the men with lower values. The estrogen levels in those with diabetes (n=21) compared with the rest (n=72) were not significantly different by *t* test, although both groups with erectile dysfunction had a similar high incidence of hypertension and atherosclerotic disease.

Potential organic etiologic factors were numerous. More than 90% of the men had at least one coexisting medical condition felt to be pertinent to their impotence. The majority (67%) took medications known to contribute to sexual dysfunction. Diuretics (used by 32 men) and β-blockers (by 18 men) were the most common. Hypertension and atherosclerotic diseases (including a history of myocardial infarction, angina, stroke or peripheral vascular disease) were also highly prevalent, seen in 51% and 42% of the subjects, respectively. Recent or past alcohol intake of six or more ounces of spirits per day was reported by 19 (20%). Stressful factors (such as marital or family problems) or psychologic disorders were elicited in 14 (15%). Three were in therapy and receiving psychoactive drugs. Earlier pelvic surgical procedures were common, consisting of fairly recent transurethral prostatectomies in 18 (19%), old vasectomies in 28 (30%) and a scattering of colonic and prostate resections and arterial bypass grafts. Three men had Peyronie's disease and six were found to have hydroceles or prior repair.

Discussion

Erectile dysfunction is a devastating problem for an affected man and his sexual partner. Since antiquity it has been a matter of concern for physicians and other health practitioners. Recently an entire sex therapy industry has developed based on the concepts from the studies of Masters and Johnson,[11] suggesting that 90% of sexual dysfunction in otherwise healthy men was of psychological origin and readily treated. We were not convinced that this was applicable to the older veterans we encountered, and in agreement with three other groups[6,8,10] we have found various organic factors in the careful evaluation of the sexual dysfunction in over 90% of our cases.

In this series, the absence of NPT in 64 of the 70 men tested added an objective measure of erectile function to the historical evidence favoring organic factors in their sexual dysfunction. Although the absence of NPT suggests an organic basis, its presence does not mean that erections during intercourse may not be impaired.[26,27] Normal snap-gauge results may also be obtained in men with abnormal erections of short duration. On the other hand, there is recent evidence that NPT may be abnormal in hypogonadism at a time when erections related to erotic stimuli are normal.[28,29]

The Derogatis inventory confirmed poor sexual functioning and dissatisfaction, although the low scores may also be explained by the fact that the tests were not standardized on elderly men with medical disorders. In spite of these deficiencies it must be noted that most of the men did not appear seriously depressed or anxious. Psychosocial stresses were identified by history in 14 of the men; however, 8 of the 10 tested had abnormal NPT, 4 of the 11 who were not in therapy and not receiving psychoactive drugs had penile blood pressure indices suspicious for vascular disease and 8 of the 14 had neuropathy. Thus, the existence of psychosocial problems does not eliminate the need to define other factors, particularly in this age group.

It is apparent that problems remain with the diagnostic evaluation for erectile dysfunction. The measurement of NPT is not a completely accurate discriminator of organic versus psychogenic disorders although it has been useful in demonstrating normal erectile capacity to patients with isolated psychogenic factors and for encouraging their participation in sexual and marital counseling or behavior modification therapies. There is presently no gold standard for evaluation of the neural role in erectile dysfunction (whether structural or neurotransmitter abnormalities are proposed). The peripheral neuropathies and absent or delayed bulbocavernosus reflexes identified in this study suggest a potential neurogenic contribution to impotence, although admittedly bulbocavernosus reflexes have not been adequately studied in the select subset of elderly men with normal erectile function, and the other peripheral sensory nerves tested play no direct role in the mechanism of erection. Clinical testing of peripheral nerve function at best correlates with general autonomic neuropathy.

While more data are available on the evaluation of penile arterial flow, the "gold standard" of pudendal arteriography is not likely to be applied as part of the impotence workup until vascular microsurgical repair becomes available as a therapeutic option. At present, there is correlation between the penile-brachial index and pudendal arteriography in that severely impaired dorsal artery flow measured by the noninvasive Doppler examination is likely to indicate a vasculogenic cause. The pressure indices may be most diagnostic when very low, indicating abnormal penile vasculature, but less helpful when normal. However, the absence of good direct cavernosal artery measurements means that much vascular disease may still go undetected.

The same conclusion may be drawn from the results of endocrinologic measurements. Obvious primary or secondary hypogonadism or hypothyroidism may be uncovered in a small subgroup of the patients. A specific role for endocrinopathy was found in only two new cases of hypothyroidism and four men with definite hypogonadism. Five additional cases of probable primary hypogonadism were found among the men with borderline testosterone. Luteinizing hormone elevation may give a clue to deficient androgen action at the tissue level; however, increasing levels with age have been reported.[30,31] Better interpretation of testosterone levels in impotence may require longitudinal studies of individual subjects' values before and after the development of impotence. Cross-sectional hormonal measurements in groups of men carefully matched for age, weight, health status, partner availability and so forth—and only differing in sexual function—are as yet unavailable.

Because there was a large degree of subject self-selection in the clinic, the incidence of hypogonadism in the general population of men with erectile dysfunction remains unknown. It is widely believed that men with androgen deficiency lack both libido and erectile function while those with other (vascular or neuropathic) etiologies usually maintain normal sexual desire while developing difficulty with erection. Patients with continued desire may be more likely to seek medical attention for their erectile disorders than those

who have lost interest in sex. Thus while endocrine disorders such as androgen deficiency and hyperprolactinemia are certainly important and reversible causes of sexual dysfunction, hypogonadism was not a frequent finding in these veterans seeking consultation specifically for sexual dysfunction. They are more likely to be detected by a primary care physician who routinely questions all patients about sexual function. Sexual dysfunction uncovered in this fashion, even (especially) in men with decreased libido, deserves systematic assessment of thyroid function, sex steroids values and prolactin levels.

The lack of relation of estrone or estradiol levels to any other measurements tended to rule out consideration of estrogen excess as a major contributor to sexual dysfunction in this group.

While excellent standards are lacking for the various diagnostic measures and potent elderly controls are needed, nevertheless, early descriptive studies as this show that older men with erectile dysfunction deserve careful interviews and examinations which may indicate the need for further physiologic tests and in some cases more etiology-specific therapy. It is crucial that physicians (generalists, internists, urologists, endocrinologists and vascular surgeons) be aware of the possible relationship between the many organic disorders they may be treating and sexual dysfunction. They must question their patients about erectile function, attempt to identify the specific pathologic condition and make an effort to find and treat the treatable organic factors as well as the psychosocial.

When the high incidence of organic impotence is explained to an older couple they may be relieved of the burden of thinking that their sexual dysfunction must have emotional causes. Further study of pathogenesis of sexual dysfunction is destined to provide substantial relief to the millions adversely affected by this syndrome.

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Lasers in Cardiovascular Surgery—Current Status

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The argon, carbon dioxide and neodymium-YAG lasers have been proposed as effective instruments for surgical procedures of the intact cardiovascular system. While argon and CO_2 lasers cause superficial (0 to 1 mm) thermal injury, the Nd:YAG laser is better suited for effecting deep thermal necrosis (3 to 4 mm). Microsurgical vessel anastomoses can be done by "tissue welding" with any of the three clinical lasers. Myocardial revascularization may be accomplished by drilling "neocapillaries" in ischemic myocardium. Endocardial resection for destroying arrhythmic pathways and removing hypertrophied septal muscle has also been successfully accomplished with laser phototherapy. Last, laser-mediated vaporization of atherosclerotic plaque in the coronary arteries and peripheral circulation may offer a percutaneous approach to the treatment of arterial occlusive disease. Cardiovascular uses of lasers are purely investigational at the current time. Much more needs to be known before widespread clinical use of lasers in the cardiovascular system can occur.

(Hunter JG, Dixon JA: Lasers in cardiovascular surgery—Current status. West J Med 1985 Apr; 142:506-510)

Laser-mediated vaporization of atherosclerotic plaque has been proposed as a method to open occluded or stenotic vessels. Media attention has created a climate of expectation surrounding this procedure, but scientific articles are becoming more tempered in their handling of laser-mediated atheroablation. In this report we will introduce readers to the biomedical laser and attempt to provide an update of what is known and what needs to be studied before lasers become standard tools of cardiologists and cardiovascular surgeons. Specifically, we will address proposed methods of intravascular laser delivery and present the experience of investigators working with lasers in the cardiovascular system.

The word laser is an acronym for *l*ight *a*mplification by *s*timulated *e*mission of *r*adiation. The first observed stimulated emission of radiation in the visible spectrum came from a ruby rod, stimulated by energy from a flash lamp.[1] Within four years the argon, carbon dioxide and neodymium-YAG lasers were developed. The ruby laser was first used by ophthalmologists in 1964 for photocoagulating the retina.[2] Goldman reported his use of the ruby and CO_2 lasers on skin in 1963.[3] Ablation of a melanoma metastasis with the ruby laser was first reported by McGuff and Bushnell in 1964.[4] At the same time, they reported an ability to vaporize atherosclerotic plaque in cadaver vessels with the ruby laser. It took 15 years of technologic evolution in lasers and fiberoptics, however, before interest was rekindled in laser therapy for cardiovascular disease.

The Biomedical Laser

From a stimulated laser medium, solid or gas, photons are emitted in the form of a laser beam (Figure 1). This beam differs from an ordinary beam of light in that all photons are of the same wavelength and are in phase with one another spatially and temporally. This is termed *coherent* light. A laser beam is characterized by its wavelength—a function of the laser medium—its focal length and its power—a function of the number of photons emitted. The beam may be directed to its target by a series of mirrors or it may be directed through a small flexible quartz fiber. Quartz-wave guides range in diameter from 100 microns to 600 microns and are readily passed through the operating channel of conventional endoscopes. The three lasers currently used in clinical medicine have as their active medium carbon dioxide, argon and neodymium-yttrium-aluminum-garnet (Nd:YAG), a crystal. Laser fibers are only available for the argon and Nd:YAG lasers at this time; however, a fiber for the CO_2 laser is currently in development.

For the most part, lasers work by heating tissue. When tissue is heated to 60°C, protein and nucleotide denaturation occur. Initially, the cell is structurally intact, though the intra-

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ABBREVIATIONS USED IN TEXT
LAD = left anterior descending [artery]
Nd:YAG = neodymium-yttrium-aluminum-garnet

cellular machinery is irreparably destroyed. At 100°C, vaporization occurs. Tissue contracts as the water is evaporated. At higher temperatures all other tissue components are sublimated, leaving only a black carbon eschar (Figure 2).

Because each laser produces monochromatic light at a different wavelength, pigmented tissue components may absorb energy from different lasers differentially. For example, hemoglobin absorbs 95% of argon laser energy in 1 mm of tissue whereas water transmits 95% of the same energy. Conversely, water absorbs more than 95% of CO_2 laser energy in 1 mm of tissue and hemoglobin transmits 90% of incident energy at this wavelength (Figure 3). Because of high absorption by hemoglobin, the argon laser is currently the best laser for treating port-wine stains and telangiectasis of the gastrointestinal tract. Similarly, darkly pigmented lesions, such as melanoma metastasis, would best be approached with Nd:YAG laser. If one can selectively stain abnormal tissue with a light-activated toxic substance (such as hematoporphyrin derivative), it may be possible to selectively destroy such tissue at energy low enough to preserve adjacent normal structures.[5]

Largely because of differences in superficial tissue absorption, each laser has a characteristic depth of injury ranging from 0.1 mm for the CO_2 laser to 4 mm for the Nd:YAG laser. Thus, in choosing a laser for a particular task, the operator must consider pigmentation of the target lesion, energy requirements and desired depth of tissue injury.

Access and Delivery of Laser Energy

Endovascular access and delivery of laser energy may be accomplished through conventional surgical exposure, fluoroscopy or endoscopy. Conventional surgical exposure ultimately provides the best control of laser energy. The major shortcoming of this approach is that many conventional surgical instruments are as good or better than lasers in an open operative field. The enduring contribution of lasers in cardiovascular surgical procedures may be the ability to operate from afar.

Percutaneous transluminal surgical procedures, such as balloon angioplasty, embolectomy and thrombus dissolution, have traditionally been guided fluoroscopically. Various investigators are in the process of developing special catheters for fluoroscopically guided intravascular laser application.[6] The common design includes a balloon for occluding a vessel and centering the catheter within the vessel lumen, a channel for saline flushing and a central channel for the laser fiber. The major problem with fluoroscopic guidance is that the operator cannot see tissue effects created by the laser. Ultimately, visual inspection of the tissue effect is the best way to guide laser energy dose. Prescribed energy doses coupled with fluoroscopic imaging are less precise ways of safely achieving desired effects.

Vascular endoscopy, or angioscopy, may provide direct vision of intravascular pathologic areas when the field is cleared of blood with proximal occlusion and the infusion of transparent flush solutions. In the peripheral circulation, a saline flush system provides good visualization and will not compromise tissue viability for the duration of most procedures.[7] In the coronary or cerebral beds, it may be possible to use a transparent emulsion of fluorinated hydrocarbons to

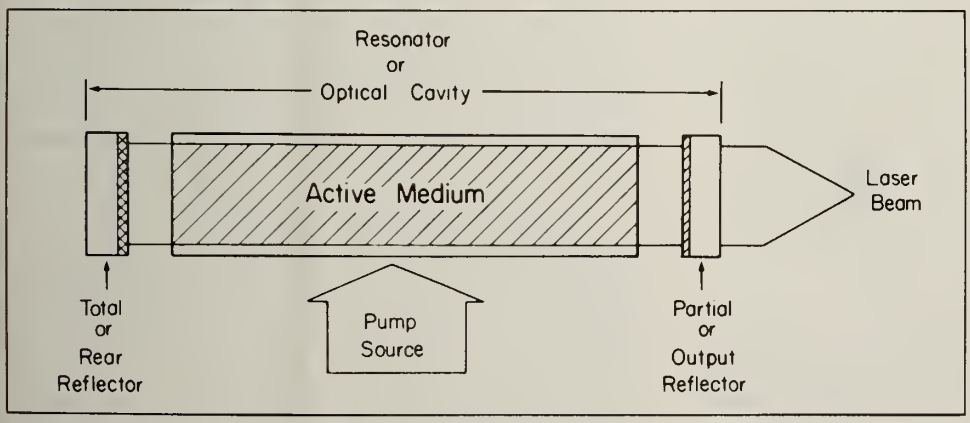

Figure 1.—Basic components of a laser. The active medium may be a gas or a crystal.

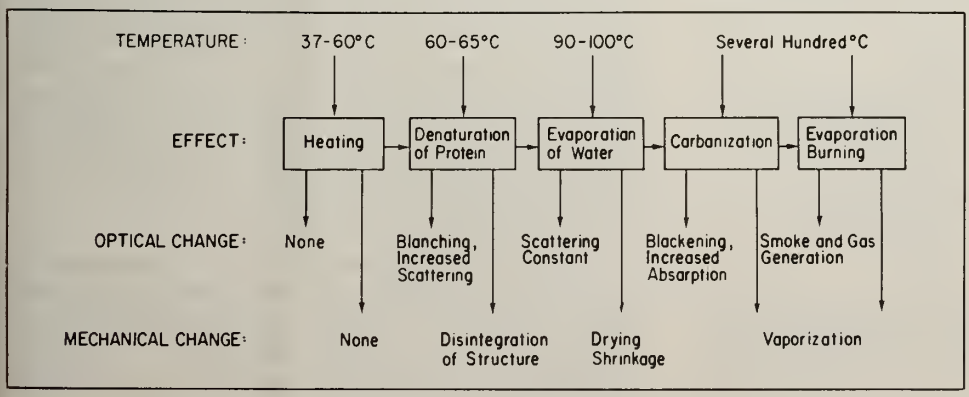

Figure 2.—Tissue effects of laser energy. Coagulation and vaporization are mediated by heating tissue to 60°C and above 100°C, respectively.

visualize vascular anatomy without compromising oxygen delivery.[8] Whether laser energy can be transmitted through fluorinated hydrocarbons is not yet known, nor has the safety of these compounds been adequately established.

There are two types of operating vascular endoscopes currently in experimental use, those with articulation and those without articulation. Lee has developed a nonarticulated operating endoscope 1.8 mm in diameter that gives access to the coronary circulation.[9] Without articulation, however, this instrument is less able to precisely deliver laser energy than articulated endoscopes. While technology currently requires articulated operating endoscopes to be at least 3.0 mm in external diameter, such an instrument is small enough to visualize the trifurcation of the popliteal artery and proximal coronary arteries. Although small vessels may be more accessible with a nonarticulated endoscope, the added precision in application given by an articulated instrument may allow more rapid and safe delivery of laser energy within the intact circulation.

Locating the target endoscopically, fluoroscopically or under direct vision is only half the battle. An instrument capable of cutting or coagulating must next be applied in a most

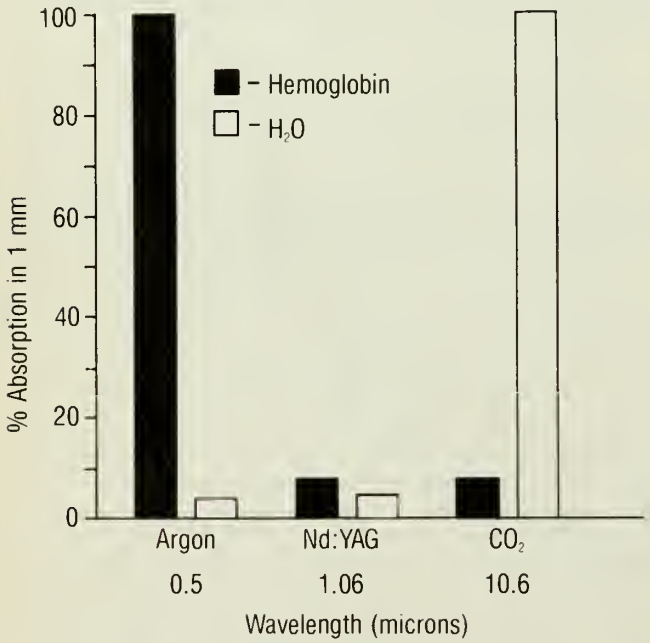

Figure 3.—Selective absorption. Argon laser is highly absorbed superficially by hemoglobin and CO_2 laser is highly absorbed by water. Nd:YAG laser penetrates deeply in tissue as superficial absorption is low.

Microvascular Welding	
3-Suture & Laser	8-Suture Technique
Time: 5-10 Minutes/vessel	15-30 Minutes/vessel
Patency: 95%-100%	95%-100%
Tensile strength: Adequate	Slightly better
Scarring/stenosis: Minimal	More frequent
Pseudoaneurysms: 0%-5%	0%-5%

Figure 4.—Microvascular laser welding. Laser-mediated microvascular anastomosis is done more rapidly and with less scarring than with conventional techniques.

controlled fashion to avoid untoward events. Lasers may provide the necessary control for many intravascular procedures.

Applications

Laser-Assisted Microvascular Anastomosis

The first successful laser-assisted small vessel repair was reported by Jain of Munich in 1979. Jain closed 50 arteriotomies and venotomies in rat vessels less than 1 mm in diameter with the Nd:YAG laser. There was no disruption and 95% short-term patency.[10] In 1965 Yahr and co-workers first carried out laser anastomosis by glueing vessels together side to side with methyl methacrylate, then perforating the glued segment with the Nd:YAG laser to open a channel between the vessels.[11] The experimental technique frequently used today for laser-assisted small vessel anastomosis requires two steps. Three microsutures are placed evenly around the circumference of the vessels to appose the vessel edges and provide tensile strength.[12,13] The laser—either CO_2 or argon—is applied to the apposed edges at milliwatt powers for milliseconds to produce a watertight seal. The advantage of this type of anastomosis is that it is fast (a standard repair of a 1-mm vessel requires eight sutures) and that it minimizes foreign body in the wound. Patency is reported at 95% to 97%, similar to that for conventional suturing techniques. There is a low incidence of pseudoaneurysms, perhaps lower than that found with suture repair.[14] The tensile strength is slightly below that of a conventional repair but sufficient to prevent disruption at systemic blood pressures (Figure 4). It is believed that the tissue glue results from collagen denaturation in the media and adventitia as well as fibrin polymerization.[12] Healing occurs with significantly less scarring.

Laser-Assisted Myocardial Revascularization

There are at least three cardiac procedures that may be done with laser techniques: myocardial revascularization, endocardial resection and transluminal laser angioplasty. Transventricular revascularization is being studied by Mirhoseini and associates. They use the CO_2 laser at very high power to drill miniature holes in ischemic left ventricular myocardium (20 to 30 holes per cm^2)[15] to reestablish perfusion to the compromised muscle. In an experimental model, the left anterior descending artery (LAD) was ligated in 24 dogs. Of those dogs, 100% treated with the CO_2 laser in the distribution of ischemia survived without electrocardiographic or histologic evidence of myocardial necrosis. Fibrillation developed in 100% of the control animals with LAD ligation alone. All died within the first 20 minutes of ischemia.

While one might think that such small "neocapillaries" would thrombose immediately, photomicrographs taken five months postoperatively showed patent laser channels and endothelialization of the channel walls. The adjacent muscle was healthy at the time the animals were killed. Mirhoseini and associates have done this procedure in one patient at the time of coronary artery bypass grafting. Postoperatively, improved contraction of the left ventricle was found.[16]

Laser-Assisted Endocardial Operations

Intracardiac surgery done from a percutaneous transluminal approach is another new area of investigation. Precise resection of valvular calcium, hypertrophic myocardium or an aberrant conduction pathway is an extreme technical challenge when done percutaneously in a full beating heart. Trans-

luminal valvular surgical procedures may be the most demanding of intravascular procedures. Lee and colleagues have reported one case of transluminal incision of a normal canine aortic valve with the argon laser.[17] More work in this area has been done in Brazil where Bozinis and co-workers have produced a canine model of pulmonic stenosis, then introduced an argon laser fiber into the right ventricle percutaneously. Using fluoroscopic guidance and a saline jet to clear the field, they were able to incise the valve and alleviate the pressure gradient without rendering the valve incompetent.[18] Isner and colleagues have reported success at excising calcium from stenotic aortic valves in vitro with the CO_2 laser.[19] Similarly, they have used the argon laser intraoperatively to resect myocardium in one patient with hypertrophic cardiomyopathy.[20]

Several investigators have reported tissue effects of lasers on myocardium[21,22] and are now developing techniques of percutaneous transluminal antiarrhythmia surgical procedures. Cardiac electrophysiologic studies done percutaneously delineate normal and pathologic conduction pathways on the endocardium.[23] Currently, pathologic circuits, such as Kent bundles or reentrant arrhythmia circuits, are addressed at the operating table if medical therapy fails. The pathway is either resected or cryoablated.[24] This treatment is effective in controlling ventricular tachycardia in a select group of patients, but the operation carries a 10% mortality and the same morbidity as a ventriculotomy. If the arrhythmia pathway can be located percutaneously and successfully treated with a freezer probe, it may be possible to interrupt the circuit with a laser or heater probe without an operation.

In preparing for ablating ventricular tachycardia circuits, Vincent and associates showed that the Nd:YAG laser introduced percutaneously could selectively destroy small portions of canine left ventricular myocardium without causing dyskinesis of the ventricle or measurable hemodynamic changes.[21] Narula and co-workers have been able to produce complete heart block in dogs by locating and dividing the His bundle with electrophysiologic study and an argon laser fiber introduced percutaneously.[25]

Percutaneous Transluminal Laser Angioplasty

A topic receiving a great deal of attention is percutaneous transluminal laser angioplasty. While most of the media attention is centered on recanalizing coronary arteries, this procedure is equally applicable to peripheral disease. It might appear that laser treatment of atherosclerosis started in the 1980s; however, McGuff and Bushnell first showed in 1964 that laser energy could destroy atherosclerotic plaque.[4] Little research was done in this field over the next 15 years, but there are now many investigators studying the effects of laser on atherosclerotic plaque and normal intima in animal models.[6,9,26-36] Only Ginsburg and colleagues have attempted to vaporize plaque in patients with peripheral vascular disease.[37] Investigational materials include atherosclerotic cadaver vessels in vitro, cadaver vessels transplanted into animals and animals prepared with atherogenic diets.

All three biomedical lasers appear to be effective in destroying plaque. McGuff and Bushnell reported their success in vaporizing fibrous and fatty plaque in 1964. They found it difficult to vaporize calcific plaque without injuring the native vessel.[4] Choy, Lee and Abela and their co-workers have reported success at vaporizing plaque and thrombus in cadaver coronary arteries.[6,9,26] Although the CO_2, argon and Nd:YAG lasers have all been used for intravascular studies, the argon laser is currently preferred because of its shallow penetration and fiberoptic delivery system. Several new laser wavelengths may be preferable to argon laser for destroying calcific plaque.

Absorption of laser energy may be enhanced by staining techniques. Abela and colleagues have used sudan black to increase absorption of Nd:Yag radiation by plaque.[27] Spears and associates reported selective uptake of hematoporphyrin derivative by atherosclerotic lesions in rabbit and monkey aortas, thus sensitizing these lesions to irradiation at 630 nm.[38] Such photosensitization of atheromata may allow complete vaporization at much reduced energy, thus sparing the vessel wall subjacent to treated plaque. Much experimental work remains to be done in this area.

The greatest concern about percutaneous laser angioplasty is its possible danger. Vessel perforation is the most lethal pitfall. Initial studies have addressed the effects of laser energy on normal vessel wall. All who have experimented with laser endarterectomy have found it easy to perforate the vessel wall with a misguided application. The energy required for vessel perforation is no greater than the energy required to penetrate fibrous plaque.[28] In most cases, perforation energy is significantly less than that required to ablate calcific lesions. In addition, the complex nature of most human atherosclerotic plaque may cause unpredictable and excessive thermal injury to vessel wall subjacent to an area of laser application.[29,30] Attempts have been made to quantify this injury. There are two major zones of injury recognized in laser applications, a zone of vaporization—the plaque, in this case—and a zone of thermal necrosis that may extend to the vessel wall. A third, less destructive zone of acoustic injury has been identified by Abela and colleagues.[27] Several experiments have shown delayed necrosis of the elastic lamina subjacent to vaporized plaque or thrombus. Van Stiegmann noted aneurysm formation in 100% of porcine atherosclerotic carotid arteries when they were subjected to enough Nd:YAG laser injury to cause full-thickness coagulation necrosis. When reimplanted in the aortic position, 75% of them ruptured. When the media was spared, there was no early perforation or aneurysm formation.[31] For percutaneous angioplasty to be successful, it will be necessary to ensure that no significant vessel wall injury occurs. For this to happen, the laser fiber will need to be close to the plaque, parallel to the vessel wall and well centered in the vessel lumen (Figure 5). The minimum energy for dissolving plaque must be used.

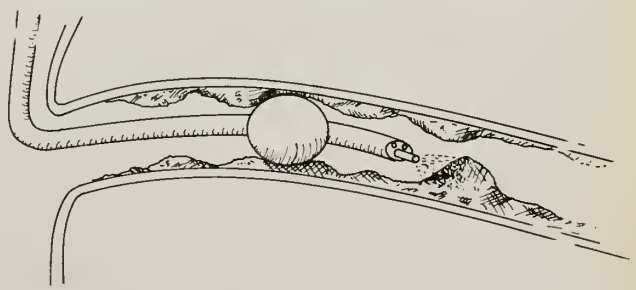

Figure 5.—Endoscopic vaporization of an atheroma. Proximal balloon occlusion clears the field of blood and centers the laser fiber in vessel lumen.

Thrombosis following laser treatment is another worry. Many investigators have shown that traumatic exposure of arterial media to the bloodstream may cause thrombosis. Will laser-denuded arterial media act similarly? Abela and co-workers found no vessel thrombosis in laser-treated canine carotid and femoral arteries despite media exposure.[32] In each case the crater made by the laser contained a fibrin/platelet thrombus, which did not project into the vessel lumen. Reendothelialization occurred within nine days. Abela and associates found the coronary arteriotomy closure to be more thrombogenic than the laser lesions. Gerrity and colleagues reported similar experience with atherosclerotic porcine aorta.[33]

While it has been well established that arterial wall trauma may accelerate atherogenesis, Gerrity and co-workers reported that porcine aortic laser burns showed no signs of increased lipid accumulation eight weeks postoperatively despite an atherogenic diet.[33] Over the same time period, atherosclerotic plaques developed in the same animals at an accelerated rate in portions of the femoral artery subjected to balloon stripping of the endothelium. No long-term studies of laser injury and atherogenesis exist.

The fear of cerebral embolism following laser treatment of carotid artery plaque has inhibited interest in this area. While no one has addressed the problem of atheroembolism scientifically, several investigators have mentioned that there was no limb-threatening ischemia or "blue toes" after laser treatment of iliofemoral atherosclerotic plaque. In the coronary bed, Choy and associates have shown that a proximally placed radiolabeled thrombus does not shower debris distally when vaporized with the argon laser. Spectrophotometric analysis showed that the products of vaporized thrombus are water vapor, CO_2 and small-chain hydrocarbons, all of which are dissolved in the serum.[6]

Conclusion

Fiberoptic technology is now available in sizes compatible with human blood vessels, and lasers are now available in many medical centers. The combination of technologies makes possible percutaneous endovascular surgical procedures. While many of the applications discussed in this review will become historical curiosities in ten years, other applications may become the standard of practice. Before the laser becomes clinically available for intravascular use, more needs to be known about the long-term effects of lasers on the heart, great vessels and peripheral circulation.

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Carinal Forceps Biopsy Via the Fiberoptic Bronchoscope in the Routine Staging of Lung Cancer

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Main carinal biopsy was carried out in 58 consecutive patients with endobronchial (endoscopically visible) bronchogenic carcinoma. Overall, the results of the biopsy were positive in 8 of 58 patients (13.8%). The biopsy results were positive in 6 of 15 (40%) patients whose carina appeared abnormal as compared with 2 of 43 (4.7%) whose carina appeared normal (P = .0025). In those patients with subtle carinal abnormalities (carinal widening or erythema) but without gross tumor involvement, the biopsy findings were positive in 5 of 14 (36%). Unlike in previous studies, a significant percentage of positive carinal biopsy findings was associated with left upper lobe lesions. There were no complications associated with the procedure. Although the yield on blind carinal biopsies (visually normal carina) with the flexible fiberoptic bronchoscope is lower than that previously reported with the rigid bronchoscope, it remains a low-risk procedure that can spare a number of patients the morbidity and expense of more invasive surgical staging when applied as a routine part of diagnostic bronchoscopy in patients with endoscopically visible bronchogenic carcinoma.

(Shure D, Fedullo PF, Plummer M: Carinal forceps biopsy via the fiberoptic bronchoscope in the routine staging of lung cancer. West J Med 1985 Apr; 142:511-513)

Accurate staging of bronchogenic carcinoma is important in determining resectability. A number of noninvasive methods have been recommended, but the lack of reliability of these techniques makes tissue confirmation mandatory.[1,2] Involvement of the main carina with mucosal or submucosal extension of an endobronchial carcinoma provides such tissue confirmation and, with rare exceptions, indicates unresectability because of the very poor prognosis associated with carinal involvement.[3,4]

A number of investigators have advised biopsy of the main carina as a routine staging procedure in patients with endoscopically visible bronchogenic carcinoma even when the carina appears normal (blind biopsy).[5-8] This recommendation is based on the finding of a significant proportion of positive results of blind carinal biopsy in patients with endobronchial carcinoma (10% to 42%).[6,8] Despite these findings, there is no evidence that routine carinal biopsy in the presence of an endobronchial tumor is a common practice today, even though the procedure may save a substantial number of patients the morbidity, mortality and expense of more invasive staging techniques.

Earlier studies showing a high yield with blind carinal biopsy were done using rigid bronchoscopes.[5-7] The only published study using a first-generation fiberoptic bronchoscope had a substantially lower yield.[8] We questioned whether this disparity was a result of disease extent at the time of initial bronchoscopy or of the different optical or biopsy capabilities of rigid bronchoscopes and first-generation flexible fiberoptic bronchoscopes. In this study we evaluate the usefulness of blind carinal biopsy as a routine staging procedure in patients with endobronchial carcinoma using a current-generation fiberoptic bronchoscope. Patients with peripheral lesions were not included in this study because previous investigators had found carinal mucosal involvement only with endobronchial carcinoma.[5,7]

Methods

In all, 58 consecutive patients who were found to have an endobronchial (endoscopically visible) lesion at the time of

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diagnostic bronchoscopy at the San Diego Veterans Administration Medical Center were entered in the study. After informed consent was obtained, the patients received atropine sulfate intramuscularly, meperidine hydrochloride intravenously and topical anesthesia with 0.45% tetracaine hydrochloride administered via an ultrasonic nebulizer. Bronchoscopy was done transnasally using an Olympus 1TR (2.6-mm channel) or an Olympus 4B2 (2-mm channel) bronchoscope. Separate forceps were used to do a biopsy of the primary endobronchial lesion and the carina. Large (2.2 mm) or regular (1.8 mm) fenestrated cup forceps were used depending on the size of the bronchoscope. At least three biopsy specimens were taken at each site, from the anterior tip, the posterior tip and the middle of the main carina. An attempt was always made to make the forceps biopsy deep enough to obtain submucosal tissue.

Before doing a biopsy of the carina, the bronchoscopist noted and characterized the appearance of the carina as normal or abnormal. An abnormal appearance was defined as gross tumor involvement (carinal involvement by the body of the tumor), widening of the carina or localized erythematous mucosal changes. The location of the primary lesion was also noted. The significance of differences between proportions was analyzed with the two-tailed Fisher's exact test.[9]

Results

A diagnosis of bronchogenic carcinoma was obtained in all 58 patients by biopsy of the primary endobronchial lesion. No complications occurred with biopsy of the primary lesion or of the carina.

The findings are summarized in Table 1. The results of the carinal biopsy were positive in 8 of the 58 patients (13.8%). The carina appeared to be abnormal by bronchoscopic examination in 15 patients and the biopsy specimen showed cancer in 6 of these 15 (40%). The carina appeared to be visually normal in 43 patients and the carinal biopsy specimen from 2 of the 43 patients (4.7%) contained cancer. The cancer in the eight positive carinal biopsy specimens included adenocarcinoma in three, squamous cell carcinoma in two, undifferentiated carcinoma in two and metastatic renal cell carcinoma in one. The difference between the proportion of positive results when the carina appeared normal versus abnormal is statistically significant ($P = .0025$).

TABLE 1.—*Results of Carinal Biopsy in 58 Patients*

Biopsy Findings	Carina Visually Abnormal No. of Patients	Carina Visually Normal No. of Patients	Total
Abnormal	6	2	8
Normal	9	41	50
Total	15	43	

TABLE 2.—*Relation of Primary Tumor Site to Positive Results on Carinal Biopsy*

Location	Positive Carinal Biopsies Number	Total Tumors Per Site Number	Percentage Positive Carinal Biopsies %
Left main stem	2	8	25
Right main stem	1	11	9
Left upper lobe	4	10	40
Right upper lobe	0	16	0
Left lower lobe	0	3	0
Right lower lobe	1	9	13
Trachea	0	1	0

Of the 50 patients who had normal biopsy results, two had small cell carcinoma and underwent no further staging, whereas seven were found to be inoperable at mediastinoscopy (tumor in paratracheal nodes). The remaining 41 underwent thoracotomy and surgical resection. The proximal margin of the resected bronchus was not found to be involved at the time of thoracotomy so the false-negative rate of carinal biopsy would appear to be low.

The distribution of tumor locations is shown in Table 2. The highest proportion of positive carinal biopsy results occurred with tumors on the left side (left main-stem and left upper lobe bronchi). The carinal biopsy findings were positive in 6 of 21 with left-sided tumors as opposed to 2 of 36 with right-sided tumors. This difference is statistically significant ($P = .042$).

Discussion

In 1945 Griess and co-workers[10] showed that significant microscopic spread of endobronchial carcinoma could occur proximal to the gross visible limits of an endobronchial tumor without producing overlying mucosal changes. This microscopic spread occurs mainly in the mucosal and outer fibrous layers of the bronchus, though tumor can also spread along the submucosal layer. When this proximal extension involves the main carina, surgical options are limited. The extensive surgical resection necessary for cure is associated with a high operative mortality and poor long-term survival and is rarely, if ever, indicated.[3,4]

The significance of microscopic spread of bronchogenic carcinoma with respect to doing a blind biopsy of the carina was later documented by Rabin and associates,[5] who found a 10.4% incidence of positive findings on blind carinal biopsies done via the rigid bronchoscope in 154 patients. The population of patients undergoing carinal biopsy in their study included patients with peripheral (not endoscopically visible) lesions and those with endobronchial lesions. Because carinal biopsy specimens never showed abnormalities in patients with peripheral lesions, the percentage of positive blind biopsies in the appropriate patient group (endobronchial lesions) was actually much higher. Waltner[6] later confirmed this result in a smaller group of patients (12), finding cancer on blind carinal biopsy in 42% of his patients. Versteegh and Swierenga[7] found a 13% positive rate also using a rigid bronchoscope. Robbins and colleagues[8] found a substantially lower rate of blind carinal biopsies (6%) but showed the feasibility of carinal biopsy through the fiberoptic bronchoscope.

The findings of our study, using the latest generation of fiberoptic bronchoscopes, agree with the results obtained by Robbins and co-workers.[8] We found a similar incidence of positive results on carinal biopsy overall (13.8% versus 10%), and a similar incidence of positive results on blind carinal biopsy (4.7% versus 6.0%). The carinal abnormalities noted in this study, like those seen by Robbins and colleagues,[8] were mostly the more subtle ones of carinal widening or mucosal erythema. Gross tumor involvement was seen in only one patient. Whether the difference in results

obtained with fiberoptic bronchoscopy and rigid bronchoscopy is due to different optical or biopsy capabilities of the instruments or to more advanced disease in the latter series at the time of initial bronchoscopy remains uncertain. Whatever the reason, the significance of these results seems clear. Carinal biopsy done at the time of initial bronchoscopy in patients with endobronchial carcinoma is capable of identifying a subgroup of patients with unresectable disease. Additional staging procedures, with their attendant morbidity and risk, become unnecessary.

It is also evident that a visually abnormal carina does not necessarily predict tumor involvement unless such involvement is extensive. In our series, 64% of those with subtle carinal abnormalities had true-negative results on biopsy. This finding is in agreement with the results obtained by Robbins and associates,[8] in which 80% of subtle carinal abnormalities proved not to be a result of tumor extension.

Our results differed from those of previous studies in the relation between a positive finding on carinal biopsy and the location of the primary tumor. Others[5,6,8] have found the majority of carinal biopsies with positive findings to be associated with primary lesions in the main-stem bronchi (left and right), followed by right-sided lobar primary lesions. Rabin and Robbins and co-workers[5,8] found no abnormalities on carinal biopsy when the primary lesion was located distal to the left main-stem bronchus, although Waltner[6] reported one case showing positive findings on carinal biopsy with an associated left upper lobe lesion. In contrast to these earlier studies, we found the majority of positive results on carinal biopsy to be in association with left-sided tumors and particularly with left upper lobe tumors in which the carinal biopsy specimen contained malignant tumor in 40%. We do not know the reason for this difference, but, considering all the studies together, it suggests that tumor location may not be a meaningful factor in the incidence of positive results on carinal biopsy. It does appear, however, that the distance between the primary lesion and the carina influences the yield of carinal biopsy. Combining the series of Robbins and colleagues[8] with our own, lesions in the main-stem bronchi had an incidence of positive findings on carinal biopsy of 21%; those in the upper lobe bronchi, 10%, and those in the lower lobe bronchi, 5%. Abnormalities on the carinal biopsy specimen have not been found in patients with peripheral (not endoscopically visible) tumors. Because carinal involvement appears to occur by direct extension along one or more layers of a bronchus, it is not surprising that peripheral lesions involve the carina less frequently.

Although the biopsy specimen of a visually abnormal carina is much more likely to show tumor involvement than that of a visually normal carina, the procedure is a low-risk one, without reported complications, and may still spare a small but meaningful number of patients more invasive surgical staging. If the procedure were applied at the time of initial bronchoscopy to the estimated 54,000 new cases of endobronchial carcinoma occurring annually,[11] 7,500 patients would be spared further surgical staging.

Forceps biopsy of the carina, which assesses mucosal or submucosal tumor involvement, does not replace transcarinal needle aspiration for staging the subcarinal nodes.[12,13] Tumor can spread from an endobronchial site to the carinal mucosa or submucosa without involving the subcarinal nodes; conversely, tumor can be present in subcarinal nodes without involving the overlying carinal mucosa.

We conclude that carinal biopsy is a low-risk procedure that should be done in patients with endobronchial lesions, particularly in those whose carina appears abnormal. Because most of the carinal abnormalities were subtle ones, some of which may be missed through interobserver variation, and because the yield with blind biopsy was small but not insignificant, carinal mucosal biopsy should probably be done in all patients with endobronchial carcinoma as a routine staging procedure, regardless of carinal appearance or endobronchial tumor location.

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Clinical Management of Field Worker Organophosphate Poisoning

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A group of 16 cauliflower workers poisoned by residues of the organophosphate insecticides mevinphos and phosphamidon was followed in weekly clinics with interviews and determinations of plasma and erythrocyte cholinesterase levels. None had preexposure baseline values. Although six had initial erythrocyte cholinesterase values within the laboratory normal range, subsequent testing showed their erythrocyte activity had been significantly inhibited. While the most severe symptoms of the 16 subjects resolved after 28 days, their erythrocyte cholinesterase levels did not reach a plateau until an average of 66 days after exposure, after which most patients continued to report blurred vision, headache, weakness or anorexia. These findings support the view that the diagnostic utility of single cholinesterase levels is limited in the absence of baseline values.

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California agriculture has a 30-year history of field worker poisonings caused by organophosphate pesticide residues. Incidents involving crews of as many as 100 or more vineyard and orchard workers have been reported.[1] There were 323 confirmed reports of pesticide residue-induced illnesses in 1983.[2] State health officials have estimated that as few as 1% of the residue-induced illnesses in field workers are reported.[1]

In the Salinas Valley of California, as in other agricultural districts, pesticides are used extensively. Local health officials received 350 physician reports of pesticide illness in 1983. Between 1980 and 1983 there were four incidents in which some 135 workers became ill from organophosphate pesticide residues on the foliage of cauliflower and lettuce plants. Since 1983 three incidents involving the drift of organophosphates resulted in 172 workers seeking emergency medical treatment.

The initial diagnosis and treatment of a cholinergic crisis are appropriately handled in most agricultural areas. In cases of pesticide applicator exposure to cholinesterase inhibitors, plasma and erythrocyte cholinesterase activities are ordinarily compared with preexposure baseline values, both to confirm the diagnosis and to decide when to release a patient for work involving possible reexposure to cholinesterase inhibitors.[3,4] However, other agricultural workers rarely have baseline cholinesterase tests. Because there is a wide variability in persons' normal cholinesterase values, the absence of baseline data makes the interpretation of single postexposure values difficult.

We followed a group of 16 field workers exposed to organophosphate pesticides to develop criteria for the diagnosis, management and return to work of organophosphate-poisoned persons who have no baseline cholinesterase values.

Report of Poisoning Event

A crew of 23 farm workers was exposed to pesticide residues in a cauliflower field in the Salinas Valley of California on July 10, 1980. The workers began their job of tying leaves over the head of the vegetable only six hours after the field had been sprayed with the organophosphate insecticides mevinphos (Phosdrin) and phosphamidon (Dimecron). The compounds are potent cholinesterase inhibitors. The oral median

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lethal dose (LD_{50}) of mevinphos is 6.1 mg per kg of body weight and the dermal LD_{50} is 4.7 mg per kg of body weight.[5] The oral and dermal LD_{50} values of phosphamidon are 24 and 143 mg per kg, respectively.[6] State regulations require a 72-hour interval between application of this combination of pesticides and reentry into the treated area.

Shortly after beginning work, crew members noticed the onset of blurred vision and eye irritation. They continued to work and over the next two hours additional symptoms of dizziness, weakness, disorientation, headache, nausea and vomiting developed. Several workers experienced cramps in their arms, legs and stomach. Two workers collapsed, one with loss of consciousness.

The two collapsed workers were driven by another exposed and symptomatic crew member to the emergency room of the Natividad Medical Center where all three were decontaminated and examined. The two collapsed workers presented with bradycardia, increased salivation, miosis and muscle fasciculations. Their serum cholinesterase values were 2.40 and 3.04 IU per liter (laboratory normal range of 8 to 18 IU per liter). The patient with the least cholinesterase activity received 1,000 mg of pralidoxime (Protopam) chloride intravenously. Both of these patients were given 2 mg of atropine sulfate intravenously and were admitted to the intensive care unit for observation. The patient who had driven these workers to the hospital received 1 mg of atropine and was admitted to the medical service for observation. His serum cholinesterase level was 6.06 IU per liter.

Thirteen other workers from this crew sought treatment on the same day from a physician recommended by the pesticide applicator. Two of these workers were admitted to hospital and the other 11 were released after plasma and erythrocyte cholinesterase determinations, with prescriptions for 2 grams of pralidoxime to be taken orally.

The remaining seven workers did not seek medical treatment on the day of the incident. One of this group, an elderly man, collapsed at home the day following his exposure and was taken to hospital. All but one of the other workers were seen by physicians during the following week.

Patients and Methods

All 23 members of the crew were invited to attend a series of follow-up clinics that began on July 21, 11 days after the incident. Initially 18 crew members joined the study but three were lost to follow-up. One additional crew member entered the study ten weeks after the poisoning.

The patients were all Hispanic and included six female and ten male subjects. Their ages ranged from 9 to 72 years, with ten patients between 18 and 26 years, three younger than 15 and three older than 34 years. One worker was five weeks pregnant at the time of exposure.

The patients had received antidotal therapy according to individual decisions of whether or not to seek medical care immediately after exposure. Pralidoxime had been administered orally to seven of the patients, pralidoxime and atropine intravenously to one person and atropine alone to two persons. The other six subjects received no antidotes.

All subjects were followed with weekly examinations. Symptoms reported by them were recorded, and blood specimens were analyzed for plasma and erythrocyte cholinesterase activity using the method of Michel.[7] Analyses were done at the same laboratory where most of the patients had

TABLE 1.—*Initial and Final Cholinesterase Values (Change in pH per Hour) of Patients Poisoned by Organophosphate Insecticide Residues.*

Patient Number	Admitted to Hospital	Received Pralidoxime	Plasma Cholinesterase Values			Erythrocyte Cholinesterase Values		
			Initial	Estimated Normal*	Percent Inhibited†	Initial	Estimated Normal*	Percent Inhibited†
Patients With First Comparable Analysis Within 1 Day of Exposure								
3	No	No	0.38	0.90	57.9	0.71‡	0.75	5.3
4	No	Yes	0.19	0.81	76.4	0.39	0.60	35.0
8	Yes	Yes	0.11	0.98	88.7	0.31	0.78	60.3
9	No	Yes	0.23	1.17	80.3	0.38	0.85	55.5
11	No	Yes	0.46‡	0.92	49.8	0.71‡	0.82	13.8
12	No	Yes	0.59‡	1.01	41.4	0.77‡	1.06	27.1
13	No	Yes	0.24	1.00	75.9	0.50	0.92	45.7
14	No	Yes	0.32	0.80	60.0	0.57	0.69	17.0
	Average Inhibition, 8 Patients				66.3§			32.5‖
Patients With First Comparable Analysis 11 Days After Exposure								
2	No	No	0.84‡	1.10	23.9	0.67‡	0.99	32.3
5	No	No	0.46‡	0.93	50.7	0.73‡	0.98	25.5
6	No	No	0.70‡	1.05	33.3	0.56	0.97	42.1
7	Yes	Yes¶	0.79‡	1.19	33.8	0.48	0.90	46.9
10	Yes	No¶	0.66‡	1.05	37.3	0.46	0.87	47.1
15	Yes	No¶	0.77‡	1.22	37.1	0.42	0.78	45.9
16	No	No	0.76‡	1.00	24.0	0.73‡	1.04	29.6
	Average Inhibition, 7 Patients				34.3§			38.5§
Patient With First Comparable Analysis 84 Days After Exposure								
1	No	No	0.63‡	0.75	16.0	0.83‡	0.87	4.6

*Estimated normal=average of last three analyses (see text).
†Percent inhibition=100−(initial value divided by estimated normal).
‡Initial value above the lower limit of laboratory normal (0.58 for erythrocyte and 0.44 for plasma).
§Inhibition was significant by paired *t*-test ($P<.001$).
‖Inhibition was significant by paired *t*-test ($P<.005$).
¶Received atropine.

cholinesterase determinations on the day of their exposure, so that the values could be appropriately compared with the initial results. They were followed until symptoms abated and three successive erythrocyte cholinesterase values showed no more than 0.02 Michel units (change in pH units per hour) increase. A case report published elsewhere presented partial data collected for workers' compensation insurance purposes.[8]

Clinical and Laboratory Findings

Cholinesterase Analyses

Normal plasma and erythrocyte cholinesterase activities were estimated for each person by averaging the last three values obtained. The initial and estimated normal activities for the 16 persons are given in Table 1. The eight persons in whom comparable cholinesterase levels were determined within 24 hours after exposure had plasma cholinesterase activity inhibited by an average of 66.3%. The difference between the initial and final plasma values for these subjects was statistically significant ($P < .001$). The erythrocyte cholinesterase activity in these subjects was, on the average, inhibited by 32.5%, a difference shown to be significant ($P < .005$).

The seven subjects for whom the first comparable cholinesterase determination was done 11 days after exposure had plasma cholinesterase depressed by an average of 34.3% and erythrocyte cholinesterase inhibited by an average of 38.5%. The fact that the initial plasma activity of these subjects was not more severely inhibited than their erythrocyte activity reflects the more rapid regeneration of plasma cholinesterase. Again, inhibition of both cholinesterases was statistically significant ($P < .001$).

The erythrocyte cholinesterase values for the 16 subjects over the course of the study are presented in Figure 1. This figure shows that the upward trend in values is apparent within the first three analyses. Regeneration was also apparent in the values of the subject enrolled in the study ten weeks after exposure.

Cholinesterase activities regenerated to 95% of the estimated normal values within an average of 57 days for plasma and 66 days for erythrocyte enzyme activity.

Rates of cholinesterase regeneration were calculated and expressed as the increase in percentage of the estimated normal activity per day. Regeneration rates for the persons followed during the first 11 days after exposure averaged 3.02% per day for plasma and 0.82% per day for erythrocyte cholinesterase. Pralidoxime had been administered to seven of these eight persons. Cholinesterase regenerated more slowly after the examination 11 days following exposure. The average rate of regeneration between this examination and the return to 95% of estimated normal activity was 0.96% per day for plasma and 0.56% per day for erythrocyte cholinesterase for the 15 subjects followed during this period.

Pralidoxime may have contributed to the higher initial rate of regeneration observed in this study; however, a more rapid rate of regeneration in the first 11 days following exposure was apparent even for the subject who had not received the antidote, indicating that there was a significant amount of spontaneous dephosphorylation of cholinesterase. There was no significant difference between the subgroups of persons who had received pralidoxime and those who had not in either the average regeneration rates or in the average number of days to recover 95% of estimated normal activity.

The slower regeneration of cholinesterase activity during the remaining convalescence is consistent with other reports that indicate that mevinphos becomes irreversibly bound to cholinesterase.[9]

The recovery of the patients' plasma cholinesterase, expressed as a percentage of individual estimated normal values, fits a logarithmic regression ($R = .91$). The regeneration of erythrocyte cholinesterase follows a linear model better than a logarithmic one ($R = .70$). These regressions are consistent with the observed recovery of cholinesterase in humans experimentally exposed to the organophosphate sarin, in whom the erythrocyte activity was restored at a rate that was constant during the period of recovery, whereas plasma cholinesterase returned at a rate that was more rapid at the outset and declined as recovery proceeded.[10]

Because subjects were followed beyond the recovery of plasma cholinesterase activity, until erythrocyte cholinesterase activity had reached a plateau of three weeks' duration,

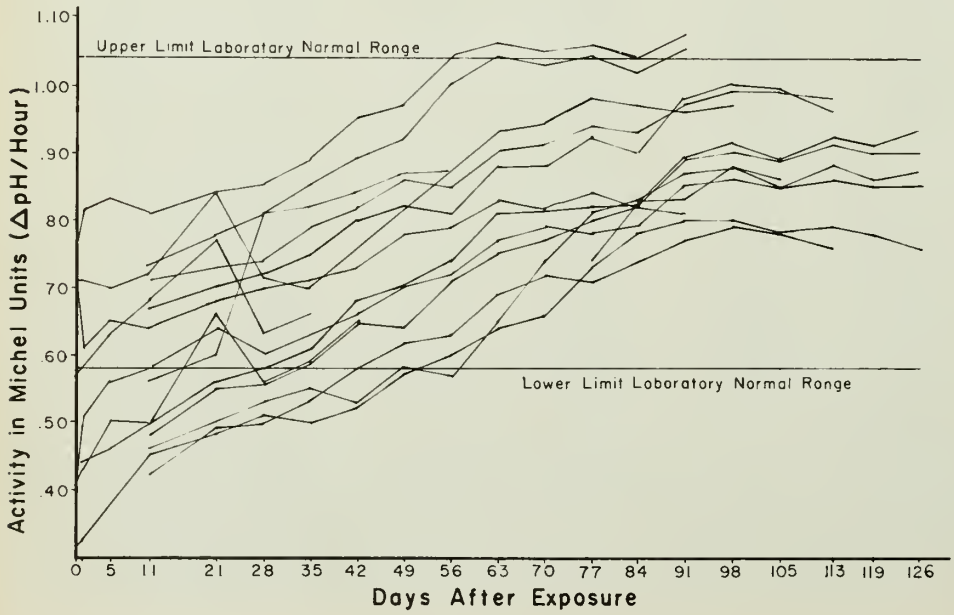

Figure 1.—Erythrocyte cholinesterase values for 16 subjects following poisoning by organophosphate insecticides.

the data allow evaluation of the postexposure period for a possible rebound effect in plasma cholinesterase activity. Some researchers have reported a rebound of 10% to 20% above normal baseline in studies of animal and human subjects exposed to organophosphates; the effect seems to occur most prominently in plasma cholinesterase levels.[11-13] This phenomenon was not apparent in the pattern of plasma cholinesterase regeneration in our study. The greatest plasma cholinesterase activity measured was no more than 3% greater than the final plasma value in any of the subjects, well within the margin of analytic error.

Clinical Findings

The symptoms most frequently reported by the patients are presented in Figure 2. Symptoms commonly associated with organophosphate-induced cholinergic excess such as nausea, dizziness, vomiting, abdominal pain and ataxia were reported by many patients initially but abated within 28 days. Other symptoms persisted throughout the entire study period in a significant number of patients. Blurred vision was one of the most common initial complaints, and reports of it persisted throughout the 18 weeks of the study. Headache, weakness and anorexia were also reported late in the study.

Prescribing the oral form of pralidoxime appears to have been ill-advised in this case. Most of the persons were nauseated or vomiting. The patient discovered to be five weeks pregnant at the time of exposure had an uneventful pregnancy and was delivered of an apparently healthy infant. A second person became pregnant during the follow-up period, had a normal pregnancy and was delivered of a healthy baby as well.

Discussion

It is commonly stated that organophosphate-poisoned persons must suffer about a 50% inhibition of plasma or erythrocyte cholinesterase activity before symptoms appear.[14] In this case, moderately severe symptoms were suffered by a group of workers whose erythrocyte cholinesterase activity appears to have been only 30% inhibited. This concurs with observations that the suddenness of decline in cholinesterase activity is more important than the absolute amount of the decline in determining whether symptoms will be manifest.[15]

It has been reported that the symptoms of patients with mild or moderately severe poisoning disappear within 24 hours and that patients with mild poisoning recover complete blood cholinesterase activity within two weeks.[14] In this case, most of the patients continued to report symptoms 70 days or more after exposure. They had regenerated 95% of their plateau plasma activity after an average of 57 days and 95% of erythrocyte activity after an average of 66 days.

It has also been reported that erythrocyte cholinesterase regenerates at a rate of 1% per day, an estimate based on the replacement rate of erythrocytes.[3] A similar rate of regeneration was observed only during the first 11 days following the poisoning; most of these persons had received pralidoxime. Erythrocyte cholinesterase from day 11 to plateau regenerated at a much slower rate, less than 0.5% per day.

This report shows many of the problems inherent in using postexposure cholinesterase values in the absence of baseline data either for diagnosing organophosphate pesticide poisoning or for determining when patients have recovered enough to return to work that may involve reexposure to organophosphate or carbamate pesticides. The laboratory normal range may not always be a useful standard for estimating cholinesterase inhibition. Because the range of normal is so wide, patients whose normal values are at the upper end of the range may lose half of their cholinesterase activity and still have values above the lower limit. As can be seen in Table 1, the initial erythrocyte cholinesterase value for 6 of the 16 patients was above the lower limit of the laboratory normal range. Subsequent testing showed that the erythrocyte cholinesterase activity in these persons was inhibited by an average

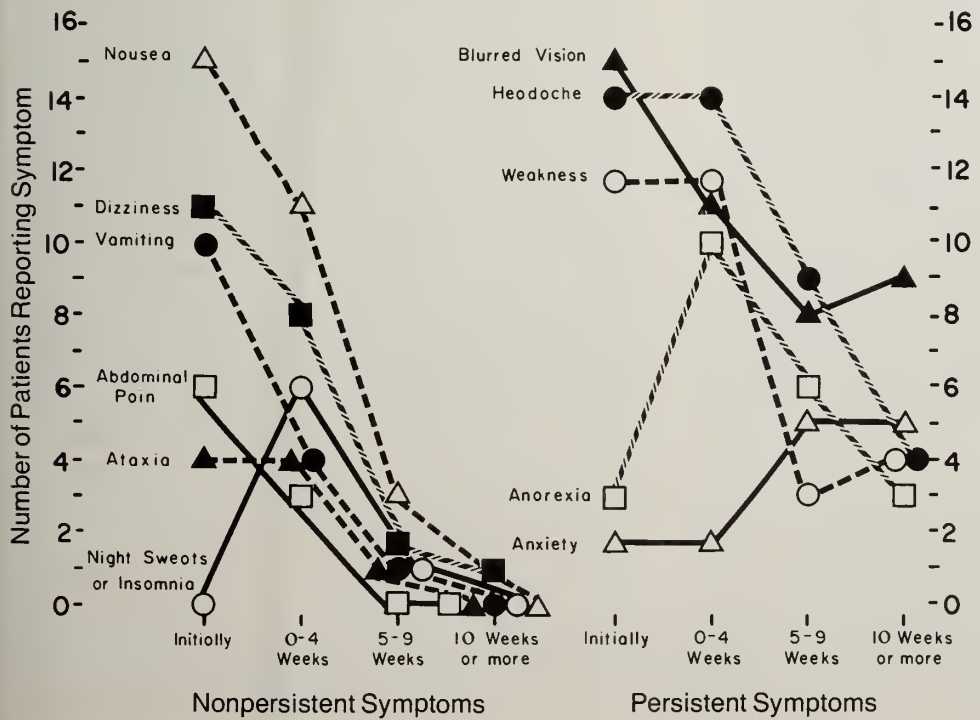

Figure 2.—Persistent and nonpersistent symptoms most frequently reported by 16 organophosphate-poisoned patients.

of 22.3%, which a paired t test found significantly different from their final erythrocyte activity ($P < .005$). This concurs with other observations that patients who suffer moderately serious organophosphate poisoning may have cholinesterase values within the lower limits of the laboratory normal range.[15]

If these workers, most of whom had nonspecific symptoms, had presented to separate physicians without a dramatic history of group poisoning (if, for example, only one worker had entered the field), the diagnosis might have been missed. Indeed, this is the dilemma that clinicians in agricultural areas routinely confront.

We suggest that sequential postexposure cholinesterase determinations may be a feasible and useful alternative to reliance on the laboratory normal range as a means to confirm cholinesterase inhibition. Sequential postexposure testing may improve the accuracy of diagnosis, provide evidence of the work relatedness of the illness for compensation and guide a physician in determining a patient's ability to work. Patients who have no baseline cholinesterase values and present with a history of exposure, cholinergic symptoms and values at the lower limits of normal should be kept from work involving any additional exposure until their cholinesterase level is retested in three to five days. Our experience in this case suggests that upon retesting, the plasma cholinesterase level should increase 15% to 20% if a significant organophosphate-induced cholinesterase inhibition has occurred. Regeneration of plasma activity is more likely to be seen over this short period because of the more rapid rate of recovery of this enzyme. Further increases on subsequent determinations would confirm the diagnosis.

Because persons with depressed cholinesterase values are especially vulnerable to poisoning by organophosphate and carbamate pesticides, it would be prudent to keep them from work involving exposure to these chemicals until their erythrocyte cholinesterase has regenerated. Erythrocyte rather than plasma values are recommended as the end point because the former better reflects cholinesterase levels in nerve tissue and, therefore, physiologic effect.[3] It is difficult to ascertain when cholinesterase activity of a patient has regenerated when there is no baseline value, however. In estimating when regeneration has been completed, consideration should be given to the fact that the erythrocyte cholinesterase activity of a healthy person may normally vary by 10% on retesting.[16] If a value increases by less than 10% over the previous value, the plateau may have been reached. Other factors that should be considered in deciding when to release such patients for work include the likelihood of reexposure to a cholinesterase inhibitor, the persistence of symptoms, whether values are at the lower limit of normal and the economic impact on patients of prolonged absence from work. This impact is only somewhat mitigated by temporary disability benefits provided by workers' compensation insurance in some states. Once patients' symptoms have abated, physicians may feel compelled to release them to work to minimize the impact of this loss of earnings, especially when the risk of reexposure is small. Patients should be advised that additional exposure before recovery is complete will entail serious risks. They should also be advised to seek medical care promptly should symptoms recur.

A more conservative approach should be taken when there is a high potential for reexposure, as was observed in this study. The work of cauliflower tying involves substantial dermal exposure to crop foliage during a time in the season when organophosphate insecticides are intensively used. The possible hazards of this occupation were underscored when a second tying crew was poisoned in September 1982. Of the 36 persons poisoned in this second incident, 6 were among the patients included in this report. A third cauliflower crew was poisoned in the Salinas Valley in April 1983.

In response to the problem of residue-induced illness, Monterey County has adopted a unique regulation requiring that warning signs be posted in fields where a worker safety reentry interval of 24 hours or greater is in effect.

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Medical Progress

Polycystic Ovarian Disease

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Polycystic ovarian disease represents a poorly defined spectrum of clinical disorders having oligo-ovulation or anovulation as a common feature. There is no single, universally accepted biochemical or clinical definition. Clinical findings usually include anovulation resulting in irregular uterine bleeding and infertility, androgen excess resulting in hirsutism and acne, and obesity. The pathophysiology involves altered functions of the hypothalamus, pituitary, ovary and adrenal glands, resulting in failure of folliculogenesis to regularly proceed to ovulation. The cause of the initiating event in this disease process remains enigmatic. Therapy for the various abnormalities in polycystic ovarian disease is tailored to a patient's needs and may include preventing endometrial hyperplasia, controlling irregular uterine bleeding, controlling hirsutism and inducing ovulation.

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There is as yet no precise biochemical or clinical definition of polycystic ovarian disease; the disease is not a single entity but a spectrum of disorders unified by the central problem of ovarian dysfunction. The diagnosis usually is made on clinical grounds, but a consensus concerning the criteria required for the diagnosis is lacking. In this discussion, the clinical spectrum of polycystic ovarian disease will be considered first; then the nature of the various hormonal and biochemical changes associated with the disorder will be analyzed. Possible etiologic factors will be reviewed and, finally, a discussion of current therapeutic modalities and their rationale will be presented.

The incidence of polycystic ovarian disease is difficult to determine. Estimates range from 1% to 4% of all women,[1] with some evidence of a familial tendency. Patients assigned this diagnosis usually present with evidence of anovulation or oligo-ovulation. They may have menstrual irregularity or infertility. The diagnosis of polycystic ovarian disease is inappropriate for patients with regular ovulatory cycles. A second major clinical characteristic is usually some degree of androgen excess, manifest as hirsutism or acne, or both. The third clinical correlation is with weight gain, obesity or difficulty in losing or maintaining weight. The extremes of these symptoms account for the classic triad of the Stein-Leventhal syndrome: amenorrhea, hirsutism and obesity.[2] Milder degrees of dysfunction in each of these categories allow for the variability in presentation mentioned above (Table 1).

There is no biochemical characteristic that is found in all women who have polycystic ovarian disease that either confirms or excludes the diagnosis. One major characteristic of this disease spectrum is an association with acyclic ovarian activity, not ovarian quiescence. It can be distinguished easily from lack of ovarian stimulation, as seen in hypothalamic amenorrhea or hypogonadotropic hypogonadism, because of the characteristic production of ovarian steroids, particularly androgens, in cases of polycystic ovarian disease. The production of estrogens (principally estrone) may cause endometrial proliferation leading to spontaneous irregular bleeding or to a positive progestin withdrawal challenge. Typically, estradiol production tends to be in the range of that seen in the early follicular phase of the normal cycle, without the increases noted at midcycle. Estrone, derived primarily from peripheral (extragonadal) conversion of androgen precursors, usually is in the high-normal range.[3] Androgens are produced in increased amounts by the ovary, often reflected in elevated circulating androstenedione and testosterone concentrations. These androgens, coupled with the small follicles and the relatively low follicle-stimulating hormone (FSH) levels, to be described later, contribute to the inhibition of the aromatase reaction in the ovary, thereby enhancing follicular atresia and inhibiting follicular maturation. The pituitary hormones are variably affected by these steroid profiles, but the pattern usually seen in patients (more than 80%) with a clinical diagnosis of polycystic ovarian disease is an increase in luteinizing hormone (LH) concentrations and an elevated LH-to-FSH ratio, usually greater than 3 to 1.[4] Proper interpretation of LH and FSH measurements requires consideration of the pronounced pulsatile release of LH that can significantly

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ABBREVIATIONS USED IN TEXT

FSH = follicle-stimulating hormone
GnRH = gonadotropin-releasing hormone
LH = luteinizing hormone
SHBG = sex hormone-binding globulin

alter the LH-FSH ratio within minutes. This can limit the clinical usefulness of a single measurement of LH and FSH levels.

Changes also may be seen in the adrenal production of androgens. Dehydroepiandrosterone and dehydroepiandrosterone sulfate are increased in many cases, as are all Δ^5-3β-hydroxysteroids; these levels are typically suppressed by the administration of dexamethasone, suggesting their adrenal origin.[5]

Some women with polycystic ovarian disease also have hyperprolactinemia,[6] which usually is associated with altered gonadotropin secretion. The hyperprolactinemia could result from the abnormal serum estrogen concentrations found in some cases of this disease, but may be a reflection of a common central abnormality, such as altered dopaminergic activity, affecting prolactin and gonadotropin secretion. Exposure of the ovary to these abnormal concentrations of pituitary hormones—that is, increased LH, decreased FSH and possibly increased prolactin—can greatly alter ovarian function. Polycystic ovarian disease also may be associated with acanthosis nigricans.

Although the histopathologic features of the ovary are variable, all ovaries in polycystic ovarian disease show signs of chronic stimulation, with many follicles in various stages of early maturation and atresia. In some cases, the ovary may be substantially enlarged with numerous microfollicular cysts and a thickened sclerotic capsule, or the ovary may be of normal size with increased stromal tissue, varying in amount from minimally increased to true hyperthecosis. Similar ovarian pathology is found in patients with other diseases resulting in anovulation, including hypothyroidism and hyperthyroidism, Cushing's disease, congenital adrenal hyperplasia and androgen-producing tumors.

TABLE 1.—*Symptoms of Polycystic Ovarian Disease*

Ovulatory Dysfunction
Amenorrhea or oligomenorrhea
Infertility
Dysfunctional uterine bleeding
Hyperandrogenism
Hirsutism
Acne
Excess sebaceous gland secretions
Anabolic State
Obesity
Difficulty losing weight

The pathophysiology of the disruption of normal cyclic ovarian responsiveness has not been established definitively. However, it is possible to explain the observed biochemical abnormalities in accordance with the known physiology of the reproductive axis. The salient features of the disease that need to be explained are the increased androgen production, the increased secretion of LH compared with FSH and the failure of folliculogenesis to proceed to ovulation.

Each of these three abnormalities in endocrine physiology can be linked together in a chain of events that perpetuates the syndrome (Figure 1). The factor responsible for the initiation of this chain of events remains unclear. The major endocrine systems involved in polycystic ovarian disease are the hypothalamic-pituitary axis, the ovary, the adrenal gland and peripheral tissues.

Altered hypothalamic-pituitary function is reflected in altered gonadotropin secretion. Several factors exist to explain the increased LH-FSH ratio. Although there is great variation in the pulsatile secretion of gonadotropins in polycystic ovarian disease, the most frequently found abnormality is increased frequency and amplitude of LH pulses. Stimulation of the pituitary with gonadotropin-releasing hormone (GnRH) results in an exaggerated LH response and minimal increases in FSH in women with this disease compared with normal women.[7] Estrogen is known to augment the LH response to GnRH. The mild tonic elevations of estrogen, predominantly estrone, in cases of polycystic ovarian disease may contribute to this altered gonadotropin release. An inhibinlike substance, which selectively inhibits FSH secretion, also may contribute to altered gonadotropin secretion. Increased inhibinlike activity has been found in follicular fluid of ovaries from women with polycystic ovarian disease when

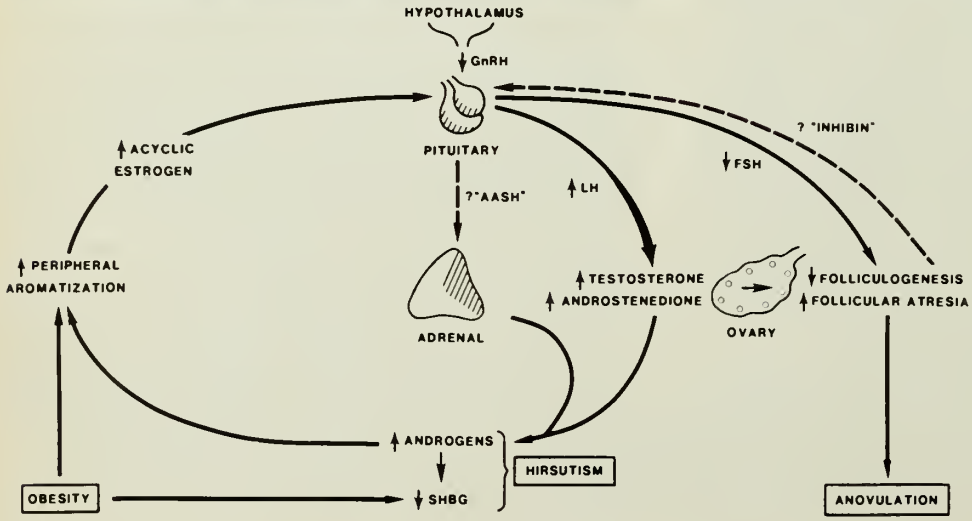

Figure 1.—This schematic shows the abnormalities in endocrine physiology that lead to the obesity, hirsutism and anovulation of polycystic ovarian disease. GnRH = gonadotropin-releasing hormone, "AASH" = adrenal androgen-stimulating hormone, LH = luteinizing hormone, FSH = follicle-stimulating hormone, SHBG = sex hormone-binding globulin.

compared with follicular fluid from similar-sized follicles in normal ovaries.[8]

Prolonged exposure to elevated LH levels may lead to hyperplasia of theca cells and increased production of the ovarian androgens, androstenedione and testosterone. Increased intraovarian androgen levels increase the rate of follicular atresia and contribute to decreased folliculogenesis by inhibiting the conversion of androgen to estrogen by enzymatic (aromatase) activity.[9] In spite of an abundant supply of androgenic substrate, polycystic ovaries have a decreased ability to aromatize androgens to estrogens. The relative deficiency in FSH and the absence of large follicles[9] are key factors in the loss of aromatase activity. Although specific enzyme defects have been reported in women with polycystic ovarian disease, the underlying cause of the morphologic and endocrinologic ovarian abnormalities appears to be inappropriate gonadotropin stimulation.

Alterations in adrenal function and steroid concentrations are found in women with polycystic ovarian disease, but their relative importance in the pathogenesis of this syndrome is uncertain. The contribution of the adrenal gland to total circulating androgen varies among different subgroups of patients with this syndrome. Elevated dehydroepiandrosterone sulfate concentrations suggest increased adrenal androgen secretion.

In the final link in the chain of events, elevated circulating androgens, principally androstenedione, are converted by aromatase in peripheral tissues such as adipose tissue to estrogens, predominantly estrone. This endogenous source of estrogen may contribute to the altered secretion of LH and FSH.

Although the total concentration of androgen and estrogen is often in the upper limits of the normal range, the peripheral effects of these steroids may be exaggerated because a larger portion of the total steroid concentration is in the free or unbound form. The reason for this increased free steroid in cases of polycystic ovarian disease is the decreased concentration of sex hormone-binding globulin (SHBG), which binds both estrogens and androgens. Both increased androgens and obesity lower SHBG concentrations.

Serum insulin levels also are increased in women with polycystic ovarian disease. Insulin resistance is known to be associated with obesity, but recent studies in nonobese women with polycystic ovaries indicate that insulin resistance in such cases may be related to hyperandrogenism.[10]

Factors, still to be defined, for initiating this chain of events may be linked to abnormal endocrine development at puberty. Careful questioning of women with this disease can often date the onset of the symptoms—that is, obesity, hirsutism or menstrual irregularity—to puberty. Theories to explain the initiation of polycystic ovarian disease include (1) an exaggerated adrenarche leading to elevated androgen levels of adrenal origin at puberty, (2) obesity resulting in decreased SHBG levels and increased peripheral aromatization resulting in an altered steroidal milieu, (3) altered central nervous system control of gonadotropin secretion and (4) enzymatic defects in either ovarian or adrenal gland (or both) steroidogenesis.

The evaluation for possible polycystic ovarian disease should include assessment of thyroid and adrenal function, measurement of circulating prolactin levels and administration of a progestin such as medroxyprogesterone acetate, 10 mg taken by mouth for 5 days, to ascertain whether bleeding occurs following progestin withdrawal. This withdrawal bleeding reflects the presence of significant circulating estrogen. Significant abnormal uterine bleeding in women older than 35 years warrants assessment of endometrial histologic appearance with an endometrial biopsy. There is an increased incidence of endometrial carcinoma in women with untreated polycystic ovarian disease.[1]

If hirsutism is a complaint, the following tests are indicated: measurement of serum androgen concentrations, of androstenedione and testosterone to detect an ovarian source and of dehydroepiandrosterone sulfate to detect an adrenal source. The presence of greatly elevated values for any of these steroids warrants further workup to rule out the presence of an androgen-producing tumor or Cushing's disease. Often serum androgen measurements are normal in spite of considerable hirsutism. Recent studies indicate that androstanediol glucuronide, an androgen metabolite, is a uniquely sensitive indicator of increased peripheral androgen action[11] and often may be elevated even with normal circulating androgens.

There are many treatment options (Table 2). The choice of treatment depends partly on the individual symptom complex, the severity of each aspect of the presenting symptoms and the therapeutic goals desired—that is, whether the primary problem is infertility or hirsutism.

When ovulation is desired for fertility, it can be induced with the use of clomiphene citrate in 80% of patients and pregnancy achieved in 40%. Those patients who do not respond to clomiphene use may be candidates for incremental doses of clomiphene, clomiphene plus human chorionic gonadotropin or clomiphene plus dexamethasone if adrenal androgen levels are elevated. The susceptibility of the ovary to cyst formation is variable and must be kept in mind during any of these regimens. Pergonal (human menopausal gonadotropins [menotropins]) or "pure" FSH can induce ovulation in clomiphene-resistant patients. Unfortunately, these patients are unpredictably sensitive to gonadotropin therapy and have a high incidence of ovarian hyperstimulation and multiple births.[12] A new alternative to gonadotropins for inducing ovulation is the manipulation of the hypothalamic-pituitary axis with the use of GnRH-pump therapy, providing pulsatile administration of GnRH on a fixed schedule. Higher doses of

TABLE 2.—*Treatment of Polycystic Ovarian Disease*

Ovulation Induction
Clomiphene citrate
+ Human chorionic gonadotropin
+ Dexamethasone
Gonadotropins
Follicle-stimulating hormone only
+ Dexamethasone
Gonadotropin-releasing hormone
Wedge resection
Abnormal Uterine Bleeding/Prevention of Endometrial Hyperplasia
Oral contraceptives
Medroxyprogesterone acetate
Hirsutism/Acne
Oral contraceptives
Spironolactone
Gonadotropin-releasing hormone analog

GnRH per pulse appear to be needed in patients with polycystic ovarian disease compared with patients with hypothalamic amenorrhea. In spite of this increased dose, there is a low incidence of ovarian hyperstimulation (E. Schriock, M. Martin and R.B. Jaffe, unpublished observations, 1984).[13] Surgical therapy (ovarian wedge resection) is occasionally appropriate for patients who have failed to respond to any of these medical forms of management, since conception rates after wedge resection are about 50%. The effects of wedge resection are frequently temporary and patients often are left with pelvic adhesions. The use of modern microsurgical techniques may decrease the incidence of this complication. However, none of these treatment modalities appears to offer a permanent reversal of the underlying disorder, and many of these patients will have only a temporary remission of the ovarian dysfunction.

The treatment of the associated obesity in the hope of restoring normal levels of SHBG and decreasing peripheral androgen production is generally characterized by frustration on the part of patient and practitioner. When ovulation is not an immediate goal and the irregularity or infrequency of bleeding is the major symptom and concern, oral contraceptives or progestin administered at periodic intervals may be used. If protection against pregnancy is not an associated objective, then many of these obese women will do well with progestin taken every second month. This prevents endometrial hyperplasia and menometrorrhagia and allows a predictable frequency of withdrawal bleeding. It also allows an opportunity for a normal cycle to intervene. Should contraception be a desired feature of therapy, then the oral contraceptives will regulate bleeding, increase SHBG production and often reduce hirsutism.

The treatment of hirsutism itself often can be accomplished with the use of spironolactone.[14] This potassium-sparing diuretic appears to act directly at the androgen receptor in addition to decreasing ovarian androgen production.

Thus, all of the above forms of treatment attempt to interrupt the pathologic chain of events of polycystic ovarian disease. Clomiphene, an antiestrogen, interrupts the tonic estrogen exposure at the hypothalamic-pituitary level. Gonadotropin therapy replaces the deficit of FSH. Giving GnRH attempts to correct the altered pulsatile gonadotropin secretion pattern. The therapeutic effect of wedge resection, though not completely understood, is probably related to a decrease in the ovarian androgen or inhibin production, or both. Oral contraceptives increase SHBG and decrease LH secretion. Spironolactone both decreases ovarian androgen production and inhibits peripheral androgen action by competing for the androgen receptor. Unfortunately, all of these modes of therapy usually have only temporary benefit.

In summary, polycystic ovarian disease is a spectrum of clinical disorders having oligo-ovulation or anovulation as a common feature. The pathophysiology is best described by a chain of events that involves the pituitary, ovary, adrenal glands and peripheral tissues as summarized in Figure 1. The initiating events are unknown, but the consequences of anovulation lead to a broad spectrum of associated symptoms and problems. Treatment should be tailored to an individual patient and is based on the symptom complex of major concern to that patient. Treatment cannot yet be directed toward permanent correction of the underlying primary disturbance.

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Specialty Conference

Photochemical Air Pollution Part II

Moderator
ELLIOT GOLDSTEIN, MD

Discussants
DONALD DUNGWORTH, DVM, PhD; ELLIOT GOLDSTEIN, MD, *and* PAOLO F. RICCI, PhD

An edited transcription of an Interdepartmental Conference arranged by the Department of Medicine of the University of California, Davis, School of Medicine.

DONALD DUNGWORTH, DVM, PhD:* The heightened contemporary interest in the toxicity of photochemical oxidants has led to many investigations with animals. These studies, in which animals are experimentally exposed to precisely measured concentrations of ozone or nitrogen dioxide (NO_2) alone, in combination or as part of a mixture of pollutants, have provided important information on the consequences of short-term or prolonged exposure to these agents. This discussion focuses on morphologic delineation of the damage caused by photochemical oxidants.

Morphologic Effects of Photochemical Oxidants on Lungs of Experimental Animals

Short-term Effects of Ozone

Depending on the ozone concentration, the short-term (less than 24-hour) pulmonary effects of exposure to ozone range from mild centroacinar inflammation at concentrations of 0.1 to 0.2 ppm[1-4] to death from pulmonary edema at concentrations above 4.0 ppm; the precise lethal concentration varies with species and duration of exposure.[5,6] Because the highest one-hour ozone concentration measured in Los Angeles between 1958 and 1977 was 0.65 ppm,[7] this discussion is limited to morphologic effects produced by ozone at concentrations of less than 1.0 ppm. Also, because ultraviolet absorption photometry is now accepted as the standard for calibrating ozone-measuring instruments, literature values based on potassium iodide calibration curves have been reduced by 80% to provide equivalent ultraviolet photometric concentrations.[8]

The most severe effect of ozone in all animal species that have been studied occurs in the centroacinar region of the lung forming the junctions between airways and alveoli.[9-14] At ozone concentrations of 0.1 to 0.2 ppm, damage is limited to this region.[2,3] Because the structure of the centroacinar region varies with species, differences occur in the exact site of the lesion. In rats, which do not have respiratory bronchioles, the lesion is in the terminal bronchioles and proximal alveolar ducts.[10,12,13] In monkeys, the lesion mainly affects the proximal orders of respiratory bronchioles.[3,14] Because the degree of development of respiratory bronchioles in monkeys more nearly resembles that in humans,[15] this is most likely the site of principal damage in human lungs. Another feature more readily appreciated in monkeys than in rodents is that the trachea and proximal bronchi are more affected than the distal bronchi, though less so than the respiratory bronchioles. This observation is in agreement with mathematical models of airway transportation and uptake of ozone.[16]

The early centroacinar response to ozone has been well characterized in rats[13,17,18] and in monkeys.[15] In rats, alveolar type I cells in proximal alveoli are most sensitive to damage. These cells become necrotic and slough within six hours after exposure to 0.4 ppm of ozone. The denuded alveolar basement membranes are covered by spreading and proliferating alveolar type II cells, which are highly resistant to damage from ozone. Ciliated cells are also sensitive, losing their cilia by two hours after exposure to 0.14 ppm of ozone. Nonciliated secretory bronchiolar (Clara) cells are less affected and, in fact, proliferate to compensate for the loss of ciliated cells by serving as their progenitors.[17,19] Inflammatory cells, mostly macrophages, appear in the lumen of affected bronchioles and alveolar ducts by six hours after

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ABBREVIATIONS USED IN TEXT

EPA = Environmental Protection Agency
FEV_1 = forced expiratory volume in 1 second
NO_2 = nitrogen dioxide

the start of an ozone exposure of 0.4 to 0.7 ppm and increase in number through 48 hours when exposure is continued.[13] The early replacement of ozone-sensitive alveolar type I epithelial cells and ciliated bronchiolar cells by alveolar type II and Clara cells is referred to as the "reparative adaptive" period[13] and is a basic pulmonary response to injury. In rhesus monkeys, an analogous sequence of events occurs in the respiratory bronchioles; the net effect is that after 50 hours of exposure to 0.64 ppm of ozone, hyperplastic and hypertrophic bronchiolar epithelium and many adherent alveolar macrophages and polymorphonuclear leukocytes are present.[4] Lesions in major airways are less dramatic than those in centroacinar regions, and damage to ciliated cells is the main change in monkeys[3,14] and in rats.[1] Thus, short-term exposure to ambient levels of ozone is clearly capable of causing morphologic abnormalities in rats and monkeys and, therefore, similar injury is likely in humans.

Intermediate to Long-term Effects of Ozone

Exposure of rats, guinea pigs and hamsters to approximately 1.3 ppm of ozone, 6 hours a day, 5 days a week over a period of 14 months produces lungs with chronic centroacinar pneumonitis and emphysema.[20,21] Exposure of rats to more relevant levels of ozone (0.16, 0.4 or 0.64 ppm, 8 hours a day, for as long as 90 days) provokes centroacinar inflammation, the intensity of which diminishes as the duration of exposure is prolonged.[22] This decrease in intensity is indicated by a reduction in the number of intraluminal mac-

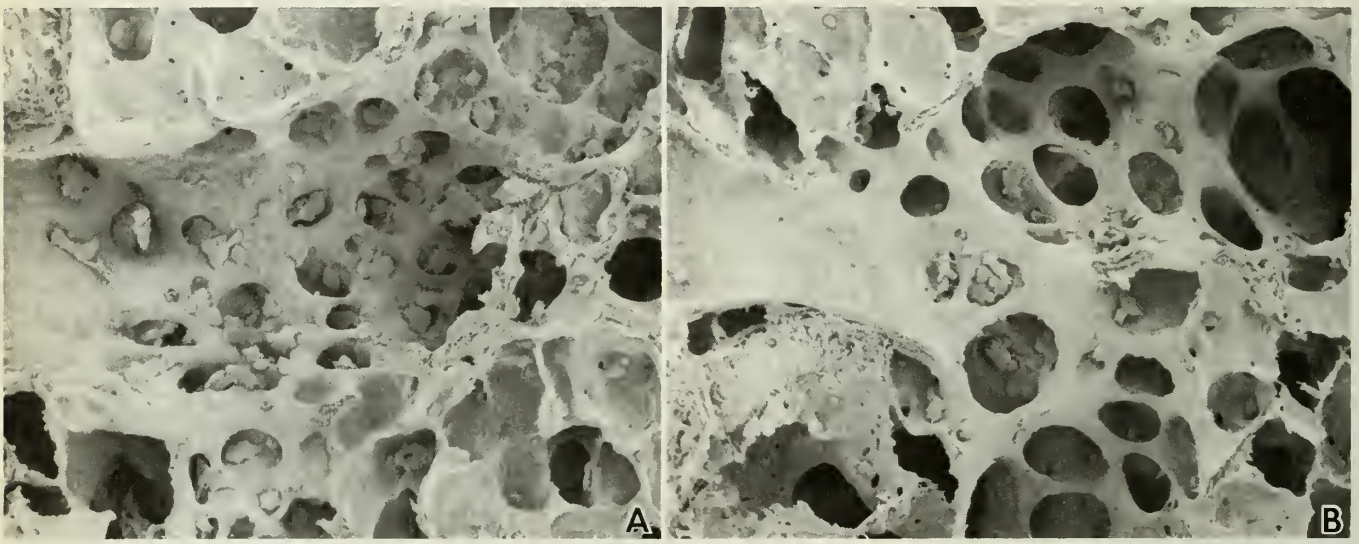

Figure 1.—A, Scanning electron micrograph of centroacinar region in lung of rat exposed eight hours a day for seven days to 0.64 ppm of ozone. Abundant alveolar macrophages accumulate in the region of the rudimentary respiratory bronchiole. **B,** A similar region in a rat exposed to 0.64 ppm ozone for 90 days. The number of macrophages is reduced compared with that of a seven-day exposure, but the alveolar ducts have undergone remodeling. Field width, 250 microns.

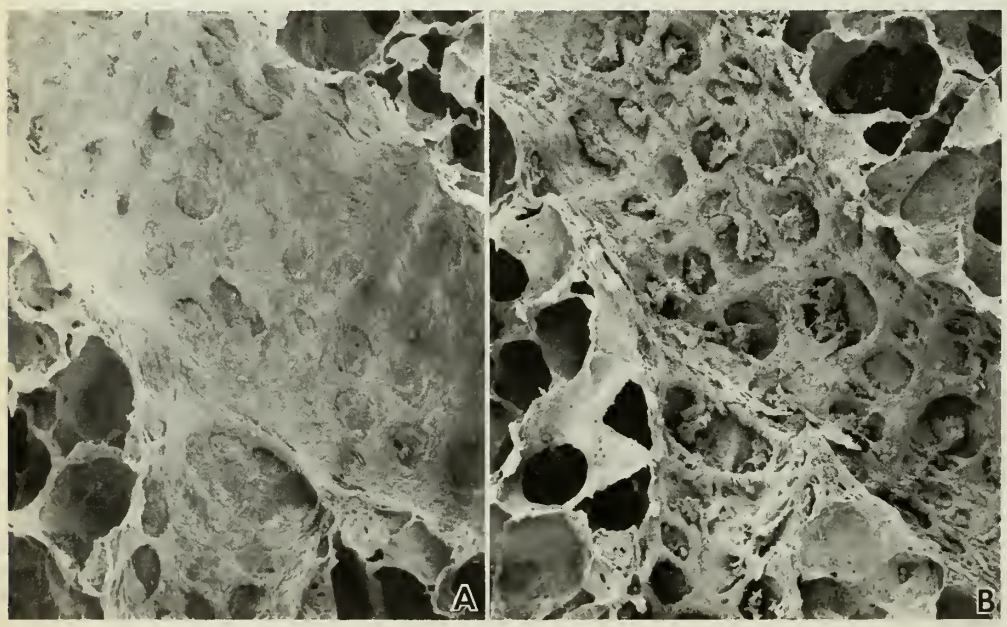

Figure 2.—A, A scanning electron micrograph of normal respiratory bronchiole of a bonnet monkey. The bronchiolar wall is lined by clusters of cuboidal cells interspersed among type I pneumonocytes. **B,** Bronchiolitis caused by exposure of bonnet monkeys to 0.64 ppm ozone 8 hours a day for 90 days. Aggregated inflammatory cells are prominent in alveolar openings and there is hyperplasia of cuboidal bronchiolar epithelium. Field width, 450 microns.

rophages and in the thickness of the blood-air barrier of proximal alveoli. After daily exposures to 0.16 ppm of ozone for 90 days, pulmonary morphology is essentially the same as in controls. At 0.64 ppm, the lesion persists but with less evidence of inflammation and epithelial damage than was present during the first 7 to 20 days of exposure. An additional abnormality of importance is the permanent remodeling of a portion of the centroacinar region to a respiratory bronchiole (Figure 1). Similar changes are found in lungs of rats exposed continuously to 0.4 ppm of ozone for 180 days.[23] Thus, prolonged exposures to ozone result in inflammation and interstitial fibrosis in centroacinar regions and some increase in total lung volume. Even though total lung volume is increased, however, the pathologic changes cannot be classified as emphysema.

Daily exposure of bonnet monkeys *(Macaca radiata)* for 8 hours to 0.4 or 0.64 ppm of ozone for 90 days also results in diminished bronchiolar inflammation at the later times.[24] The hypertrophy and hyperplasia of the bronchiolar epithelium are maintained, but the amount of fibrosis is minimal (Figure 2). After one year of exposure to 0.64 ppm of ozone for eight hours a day, the lungs of bonnet monkeys show a chronic bronchiolitis that is only slightly more severe than that noted at 90 days; they also show a greater number of inflammatory cells and narrower bronchiolar lumens.[25] These more severe abnormalities account for the small but significant increases in airway resistance and the corresponding decreases in forced expiratory volume in one second (FEV_1) observed after one year of exposure.[26]

Effects of Nitrogen Dioxide

Experiments with a wide variety of animals indicate that exposure to very high levels of NO_2 is required to produce death.[27,28] In mice, rats or guinea pigs, the threshold level of mortality following a one-hour exposure to nitrogen dioxide is 40 to 50 ppm.[27] Rabbits and dogs are more resistant,[27] as are monkeys, which survive exposures of eight hours to 65 ppm of NO_2.[28] Brief exposures to high concentrations of NO_2 are much more toxic than equivalent exposure to low concentrations of the pollutant for prolonged periods.

Lesions occur primarily within the lung in animals exposed for less than 24 hours to high levels of NO_2.[27] All species have varying degrees of vascular congestion, edema, bronchiolitis and parenchymal inflammation.[28-31] Short-term exposure to nearly ambient concentrations of NO_2 (2 to 3 ppm) does not result in serious canine or murine morphologic abnormalities.[31,32] At these concentrations, ultrastructural and scanning electromicroscopic studies show losses of cilia, swelling and disruption of type I alveolar cells, fibrin deposition along basement membranes and influxes of macrophages.[31,32] These lesions are transient, and if the insult is discontinued, the damaged tissue is repaired. These and similar results indicate that exposure to nearly ambient concentrations of NO_2 does not provoke pulmonary lesions of the type induced by ambient concentrations of ozone. In fact, it is generally stated that short-term exposure to NO_2 is 1/10th to 1/20th as toxic as to ozone.[33-35]

All animal species studied survive continuous exposure of a year or more to levels of NO_2 of at least 0.5 ppm.[36-41] Mice survive exposure to 0.5 ppm for 12 months,[36] rats survive 0.8 and 2.0 ppm for a lifetime,[37,38] dogs survive 5.0 ppm for 15 months,[39] squirrel monkeys *(Saimiri sciureus)* survive 1.0 ppm for 16 months[40] and stump-tailed monkeys *(Macaca arctoides)* survive 2.0 ppm for 2 years.[41]

Prolonged exposure to ambient concentrations of NO_2 does not appear to cause significant morphologic damage. The lungs of mice, the species most susceptible to nitrogen dioxide-induced injury, show changes consisting of shortening of cilia, edema and proliferation of alveolar epithelial cells following one-month exposure to 0.5 ppm of NO_2.[42] The lungs of rats exposed for their entire lifetime to 0.8 or 2.0 ppm of NO_2 show only ciliary loss, epithelial hypertrophy and "cytoplasmic blebbing."[37,38] Similarly, the lungs of stump-tailed monkeys exposed for 14 months to 2.0 ppm of NO_2 show only hypertrophy of bronchiolar epithelium.[43] Evidence that NO_2 might not be as innocuous as these reports indicate, however, is the finding of mild but functionally detectable emphysema in the lungs of beagles exposed 16 hours a day for 68 months to a combination of 0.63 ppm NO_2 and 0.25 ppm nitrogen oxide with morphologic evaluation after an additional three years in clean air.[44] When animals are exposed long term to much higher concentrations of NO_2 (8.0 ppm and higher), destructive changes in alveolar walls and abnormal enlargements of distal air spaces occur, which resemble emphysematous lesions in humans.[45-47] Because of the high concentrations used in these experiments, the results cannot be extrapolated to NO_2 exposures in humans.

Morphologic Aspects of Adaptation

The term adaptation refers to several different aspects of ozone-induced effects: reduction of airway irritability responses in human volunteers exposed sequentially, protection of experimental animals against death from acute pulmonary edema and alteration of the time course of centroacinar inflammation in experimental animals. Anatomically, the long-term effects of ambient levels of ozone are limited to the centroacinar regions in animals and there is reason to expect that this is the case in humans. Adaptation of importance relative to the risk of long-term effects in humans must be analyzed in terms of cellular changes in this highly vulnerable centroacinar region. Evidence has been presented that the intensity of centroacinar inflammation diminishes during daily exposures to 0.64 ppm of ozone in rats over a period of 180 days[22,23] and in bonnet monkeys over a year.[24,25] At lower levels (0.16 ppm) of ozone, inflammation almost disappears. Thus, adaptation is a transient response to persistent injury, and maintenance of the adaptive state requires continuous or frequently repeated exposure to ozone.[48] Although the pathophysiology of the adaptive state in which sensitive cell types are replaced by resistant ones is unknown, the effect is protective in that the rate of cumulative damage is less than it would be without adaptive changes. Thus, adaptive changes reduce the intensity of bronchiolitis, thereby diminishing the extent of permanent injury produced by a smoldering lesion.

In summary, extensive morphologic investigations have been carried out in animals of short-term and long-term exposures to ozone and nitrogen dioxide. These studies have shown that short-term exposure to ambient concentrations of ozone produces cellular changes and subtle structural abnormalities in pulmonary centroacinar regions of rodents and nonhuman primates; prolonged continuous exposures for up to one year to peak ambient levels affect the same regions,

producing mild bronchiolitis and interstitial fibrosis. Because these lesions are associated with only small physiologic disturbances in nonhuman primates, uncertainty exists regarding the importance of the lesions detected at lower levels of exposure. Ascertaining the importance of these oxidant-induced lesions is an area for future investigation. Similar studies of animals exposed to ambient levels of NO_2 do not show morphologic abnormalities, regardless of the length of exposure.

Effect of Photochemical Oxidants on Susceptibility of Animals to Pulmonary Bacterial Infection

ELLIOT GOLDSTEIN, MD:* Recognition of the association between exposure to ozone or NO_2 and the development of respiratory infection has resulted in the use of animal models of infection to evaluate this pathophysiologic relationship.[49,50] As a surrogate for the process in humans, animal models that show the physiologic interaction between bacteria and host antibacterial defense systems have a number of virtues that provide bases for extrapolation. Animal and human antibacterial defenses consist of an aerodynamic filtration system, transport mechanisms for removing bacteria, phagocytes (alveolar macrophages and, when required, polymorphonuclear leukocytes) and immune secretions of lymphocytes and plasma cells. In rodents and humans, these components act in concert to maintain the lung free of bacteria.[49-52]

The aerosol model in which rodents inhale bacteria and in which measurements are made of rates of physical removal and intrinsic bacterial killing permits testing of the aforementioned components as well as the entire antibacterial system.[49,50] When this rodent model is used, the animals are exposed for variable periods to different concentrations of photochemical oxidants, and decreases in antibacterial activity reflect quantitative impairments in function. Because of the similarities of human and rodent defense systems, impairments observed in rodents presumably occur in humans, and although quantitative dose-response extrapolations cannot be made from the rodent data, qualitative conclusions are justified. That is, the identification of a pollutant-induced defect, such as an inability of alveolar macrophages to kill inhaled bacteria or a delay in mucociliary clearance, indicates that the abnormality may be expected in human exposures.

When mice are infected with *Staphylococcus aureus* and then exposed for five hours to increasing concentrations of ozone beginning at 0.62 ppm, the ability of the alveolar macrophage to eradicate the invading microbe is progressively impaired.[53] This abnormality is due primarily to diminished intercellular killing of ingested microorganisms and secondarily to reduced rates of ingestion.[54] As a result of these abnormalities, staphylococci that normally do not replicate within alveolar macrophages proliferate, destroying the phagocyte (Figure 3).[54,55] When the same animal model is used to study NO_2, progressive impairments in bacterial killing are first noted after a four-hour exposure to 7.0 ppm of NO_2, showing the lesser toxicity of this pollutant compared with ozone.[56] More prolonged exposures to NO_2 produce impairments in bacterial killing at lower concentrations (2.0 ppm), confirming the cumulative toxicity of NO_2.[56] At threshold concentrations for inducing abnormalities in phago cytic function, neither ozone nor NO_2 causes serious impairment in mucociliary clearance rates.[53,57,58] Thus, both ozone and NO_2 can inhibit the capacity of alveolar macrophages to maintain pulmonary sterility, thereby rendering the lung vulnerable to bacterial infection; moreover, consistent with previous conclusions, at nearly ambient levels short-term exposure to ozone is much more toxic than is short-term exposure to NO_2.

Coffin and Blommer,[59] Ehrlich,[60,61] Gardner[51] and Gardner and Graham[62] have extended these pathophysiologic observations by developing a rodent model, often referred to as the "infectivity model," linking interference with antibacterial activity to mortality. Instead of infecting rodents with minimally virulent staphylococci, these investigators expose

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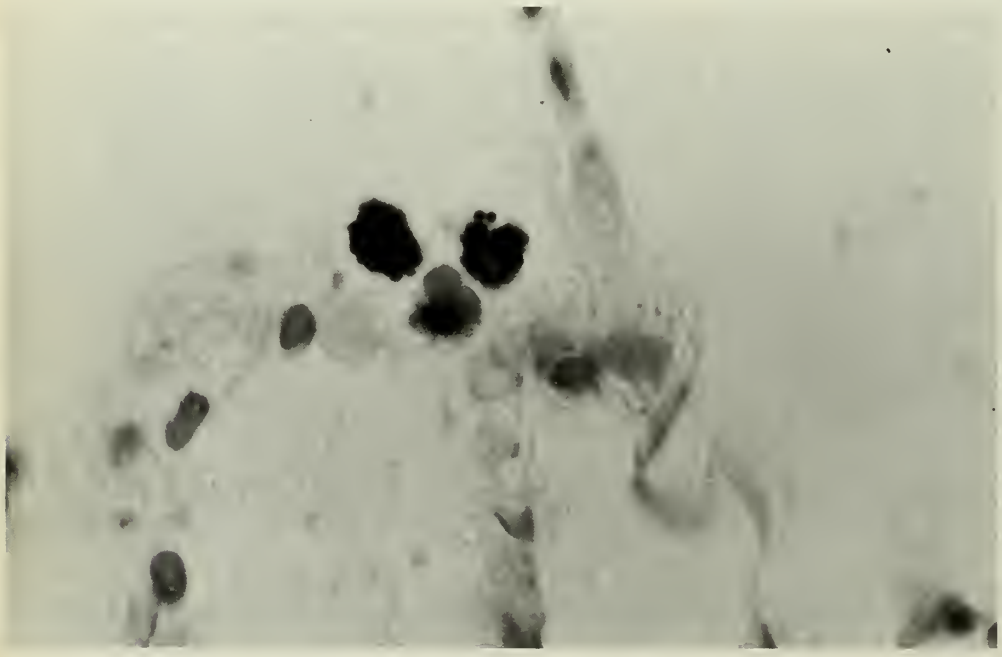

Figure 3.—Two large clumps of staphylococci that appear to be growing out from unidentified cells of the pulmonary alveolar region. The specimen is from a rat exposed to 2.5 ppm of ozone for four hours. (Brown-Brenn stain, reduced from magnification × 2,200.) (Reproduced with permission from Goldstein et al.[54])

the animals to highly virulent group C streptococci[59,62] or *Klebsiella* species[60,61] before or following pollutant exposure. When these pathogens are used, the pathophysiologic alterations in antibacterial defenses induced by the pollutant result in bacterial proliferation and excessive mortality. These investigations have shown that two-hour exposures to ozone concentrations as low as 0.1 ppm increase murine mortality from group C streptococcal infections[59] and that exposure to NO_2 concentrations as low as 3.5 ppm increases murine mortality from klebsiellal infections.[61] The infectivity model has also been used to show that one- to two-hour exposures to much higher concentrations (5 to 25 ppm and 50 ppm) of NO_2 are required to kill infected hamsters and squirrel monkeys, emphasizing the differences in susceptibility to pollutant toxicity among species.[63] Thus, results with aerosol models of infection show that short-term exposures to ambient levels of ozone but not NO_2 impair normal pulmonary antibacterial defenses by interfering with the capacity of alveolar macrophages to kill inhaled bacteria and are associated with increased mortality. Furthermore, insofar as these results can be applied to humans, they suggest that short-term exposures to ambient levels of ozone may adversely affect the function of human alveolar macrophages.

Long-term Effects of NO_2

The few studies in which the effect of prolonged exposure to ozone or NO_2 on murine capacity to survive aerosol challenges with virulent group C streptococci or *Klebsiella pneumoniae* has been assessed have shown pollutant-induced increases in mortality similar to those observed in short-term studies.[64,65] Mice exposed to peak daily doses of 0.2 ppm of ozone or 0.94 ppm of NO_2 for three hours per day have increased mortality when challenged with group C streptococci following six but not three months of exposure.[64] The threshold level for NO_2-induced mortality in the infectivity model is in the range of 0.38 ppm of NO_2, which did not produce increased mortality following nine months of continuous exposure (group C streptococci),[64] and 0.50 ppm, which caused increased mortality after three months of continuous exposure *(K pneumoniae)*.[65] When exposures are to both pollutants, an additive effect is sometimes observed.[64,66,67] Viewed in relationship to ambient concentrations of ozone and NO_2, these results are in accord with previous findings that ambient levels of ozone but not NO_2 impair pulmonary systems.

In the above studies healthy animals were used that were infected before or following the pollutant exposure. Because humans with underlying pulmonary infections may be especially vulnerable to oxidant-induced injury, animal models with chronic infections are needed to assess the role of photochemical oxidants as an aggravating insult.[68,69]

We recently tested the effect of a four-week exposure to 0.64 ppm of ozone in one such model in which a smoldering *Pseudomonas* infection was produced by intratracheally instilling *Pseudomonas*-containing agar beads.[70] Although the pollutant caused anatomic damage, the infection itself was unaffected, indicating that the pollutant does not inhibit antibacterial defenses when infecting bacteria are confined within granulomas. Future studies with animal models mimicking nongranulomatous bronchial infections, such as those produced by *Legionella pneumophila,* are needed to further define the effect of long-term exposures to ambient levels of photochemical oxidants on a chronically infected lung.

In addition to potentiating infection, photochemical oxidants may act as mutagens.[71-74] Chromosomal changes have been reported in circulating lymphocytes of Chinese hamsters following five-hour exposures to 0.2 ppm of ozone[73] and in lymphocytes from humans exposed for six to ten hours to 0.5 ppm of ozone.[74] However, in other studies carried out in nearly identical fashion in mice and humans, cytogenetic damage was not detected.[75,76] Because of these conflicting results, the mutagenic potential of ozone for animal cells is unproved. When compared with known mutagens like ultraviolet light and x-rays in eukaryotic systems, ozone acts as a weak mutagen, suggesting that the genetic risk, if it occurs, is small.[77]

NO_2, by virtue of its capacity to form nitrites, can convert secondary amines to carcinogenic nitrosamines.[78] Iqbal and co-workers reported that microgram amounts of *N*-nitrosomorpholine were produced in mice gavaged with morpholine and then exposed to 0.2 to 50 ppm of NO_2 for four hours.[79] These results were confirmed by van Stee and colleagues,[80] who have also shown a marginally significant increase in the incidence of pulmonary adenomas in CD-1 mice exposed to 1 to 2 ppm of NO_2 for 6 hours daily, 5 days per week for 30 weeks while ingesting morpholine from drinking water.[81] Because of the artificial conditions of these experiments and because malignant tumors have not been observed in mice or hamsters exposed to 4.0 ppm of NO_2 for as long as 16 months, the biologic significance of these controversial studies is uncertain.[82,83] This is an active area of research in which future studies should result in more definitive conclusions of the carcinogenic potential of nitrogen dioxide.

In summary, studies of the effect of short-term exposure to ambient concentrations of ozone in rodent models of infection show that the pollutant inhibits the capacity of alveolar macrophages to kill intrapulmonary bacteria and that virulent bacteria proliferate and kill the host as a result of this abnormality. Whether these adverse effects occur in humans is unknown, but because infection is a conceivable consequence of exposure to ambient concentrations of ozone, this adverse effect is of potential importance. NO_2 also inhibits the ability of alveolar macrophages to kill inhaled bacteria. This pollutant, however, is less toxic than ozone, requiring exposure conditions much above ambient levels. Studies of the mutagenic and carcinogenic potential of these pollutants show that ozone is a weak mutagen in eukaryotes and that its mutagenicity for human cells is uncertain. NO_2, in experimental situations differing significantly from environmental conditions, reacts with secondary amines to form potentially carcinogenic nitrosamines. The significance of these observations for human exposure is unknown.

Cost-Benefit Estimates for Controlling Photochemical Oxidant Pollution

PAOLO F. RICCI, PHD:* Because photochemical oxidant pollution is a humanmade problem, it is readily controlled by reducing emissions from mobile and stationary sources. This salient fact is the basis for the Clean Air Act requirement that primary national ambient air-quality standards be determined

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solely as a function of health risk. (In analyzing the National Ambient Air Quality Standards provision, the Supreme Court held that "claims of economic or technological infeasibility may not be considered by the Administrator in evaluating a state requirement that primary ambient air quality standards be met in the mandatory three years."[84]) To accomplish this objective, the Environmental Protection Agency (EPA) established standards for photochemical oxidant and nitrogen dioxide on health-risk assessments alone and then promulgated regulations to achieve these standards. Specifically, NO_2 emissions that averaged more than 3 grams per mile in gasoline-powered automobiles in the 1970s were limited to 2 grams per mile in 1980 models and to less than 1 gram per mile in present models.[85] Allowable NO_2 emissions from fossil-fuel power plants, which had increased from 5.8 to 6.8 million metric tons per year from 1970 to 1978,[86] were set in the most recent source-performance standards at 0.5 to 0.8 lb per million British thermal units, depending on the type of coal.[87] Because these regulations were designed to maximize protection, they were costly but consistent with the intent of the mandate of the Clean Air Act.

However, as we have become aware of the finite nature of our resources, the policy of eradicating risk to the greatest extent possible has been declining in popularity, and considerations of societal benefit versus societal cost have replaced demands for a technologically risk-free society.[88] Accordingly, in decisions involving environmental control, the benefits of control strategies are now weighed against the economic impact on transportation and energy industries. In the following discussion I will review economic information on the cost-benefit balances involved in these photochemical oxidant and NO_2 issues.

In recent years, the cost of reducing nitrogen dioxide emissions of mobile and stationary power plant sources has been assessed economically.[89,90] According to figures released by the EPA, the annual cost for mobile-source pollution control was slightly less than $6 billion in 1977 and represented 0.25% of the 1977 gross national product.[89] In future years, if the strictest standards of the Clean Air Act—particularly the NO_x standard of 0.4 gram per mile—are enforced, the annual cost will reach $11 billion.[90] As an example of individual costs, automobile purchasers paid an extra $480 for emission control equipment to achieve the nitrogen dioxide standard of 1.0 gram per mile on 1981 models.[85] Additional annual expenses were incurred in lessened fuel economy, which in 1977, when gasoline was $0.35 a gallon, averaged $13.70, and maintenance, which for the same year averaged $7.50.[91] These costs allow a 94% reduction in emissions from the 1960 level and, as is shown in Figure 4, further reductions in nitrogen dioxide emissions will be even more expensive, owing to the exponential increase in cost.

The investment cost to the fuels and energy industry in reducing air pollution is estimated at $3 billion per year for the period 1977 to 1981. The removal of sulfur oxides and particulates with nitrogen dioxide accounts for approximately $300 million of the annual estimate. The $300 million represents $5 to $10 per kW of installed capacity, which is less than 1% of the total cost of the electricity generated.[92] These costs apply for the least expensive, low NO_2 burner, abatement technologies. More expensive technologies, like flue gas denitrification, have a capital cost of $35 to $45 per kW installed capacity, which is 4% to 8% of the total cost of the generated electricity.[92] Newer methods such as the Hitachi-Zosen system, which uses a postcombustion process to achieve a 90% efficiency in removing NO_2, are even more costly, ranging from $65 to $95 per kW installed capacity.[93] Thus, if further reductions in stationary-source emissions of NO_2 are demanded, in the absence of improved technology, the expense is likely to increase considerably.

As is apparent from the previous discussions of the health effects of photochemical oxidants, the benefits obtained by

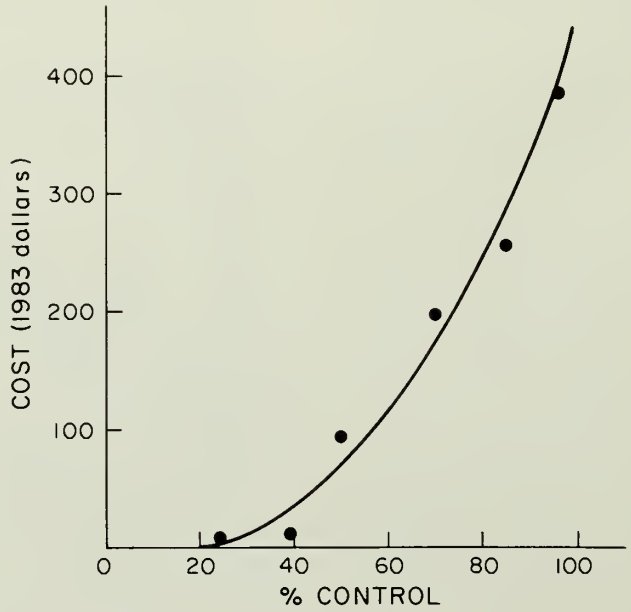

Figure 4.—Cost-control relationship for nitrogen dioxide. (Modified from Schwing et al[91] by the gross national product price deflator [1970 = 91.4; 1983 = 213.4, first quarter].)

reducing NO_2 emissions are fraught with uncertainty. Most analysts have assumed that mortality and morbidity are consequences of exposure to ambient levels of photochemical oxidants.[90,91] When these assumptions are used, the benefits of total abatement of NO_2 pollution vary between $183 million and $1.6 billion for mobile-source emissions in some studies to as much as $1.5 to $5 billion in other studies, which included material damage.[94] Assessing stationary-source benefits from eliminating NO_2 emissions is even more uncertain because of the role of other pollutants like sulfur dioxide, particulates and carbon monoxide.[95] Benefits from preventing agricultural losses due primarily to ozone are estimated to be $100 million per year in the south coast air basin of California, an area with high photochemical pollution and high agricultural production.[96] Nationwide benefits are estimated to be $278 million (EPA, unpublished data, cited by Leung and co-workers[96]).

Although considerable uncertainty exists in determining the cost-benefit relationships, some experts consider the costs in controlling photochemical oxidants to exceed the benefits.[90,91,97] The annual costs computed by these economists for controlling mobile-source emissions are upwards of $5 billion per year, an amount in excess of their estimates of benefit. However, intangible nonmarket benefits such as diminished sensory discomfort and annoyance and increased pleasure from the enjoyment of a cleaner environment are not included in these estimates.[91] Much of the public is willing to pay for these intangible benefits, and in recent years this number has increased, so that those nonmarket benefits are assuming increased importance.

Summary

ELLIOT GOLDSTEIN, MD: Several conclusions can be drawn from the preceding presentations. First, results from volunteer studies, epidemiologic investigations and animal experiments show similarities in threshold for ozone-induced photochemical oxidant effects. Short-term exposures to levels of 0.3 ppm or greater are clearly detrimental to health, causing respiratory symptoms and diminished ventilatory function. Exposure to lower levels (0.12 to 0.3 ppm), which occur often in heavily polluted areas like the Los Angeles basin, are associated with a higher prevalence of respiratory symptoms, impairment in exercise tolerance and possible increases in incidence of asthmatic attacks and reductions in ventilatory function. Although animal models suggest that these levels enhance susceptibility to infection, no data from studies in humans support such an occurrence. Exposure to lower concentrations of ozone does not cause disease, dysfunction or discomfort, even in hypervulnerable populations. Thus, the present standard of 0.12 ppm of oxidant for a one-hour period is at or beneath the probable-effects level for photochemical oxidant injury. The margin of safety, however, is small, and future studies may show that some persons are vulnerable to injury from 0.12 ppm of ozone.

Second, the available information indicates that discomfort and impairment during athletic activities are the likeliest consequences of short-term exposure to oxidant concentrations at the present 0.12 ppm standard. Athletes in competitions requiring strenuous activity, such as bicycle riding or distance running, may not do as well when photochemical oxidant levels reach 0.12 ppm. Because we are a sports-minded country, a deleterious effect of this kind has enormous social importance.

Third, because of the paucity of epidemiologic data correlating prolonged exposure to photochemical oxidants with disease, dysfunction and discomfort, the risk for populations living in heavily polluted areas is uncertain. Studies do not show an increase in disease incidence or enhancement of underlying pulmonary illnesses as a result of pollutant exposure. Small reductions in ventilatory function and increased incidence in self-limiting respiratory symptoms are possible consequences of such exposures, but definitive proof is lacking. This lack of effect from exposure to ambient levels of photochemical oxidants agrees with results from studies in animals showing only modest cellular defects following similar exposures. However, because of the importance of definitively determining the risk to humans from long-term exposure to photochemical oxidants, attaining conclusive epidemiologic data should be a major goal of health agencies. The magnitude of the health and economic considerations involved in establishing standards for photochemical oxidant exposures mandates that despite their difficulty, epidemiologic studies should be concluded within this decade to determine the risk.

Fourth, an abundant body of evidence from studies with volunteers, exposed populations and animal models indicates that short-term exposures to ambient levels of NO_2 do not cause disease in healthy persons or aggravate underlying pulmonary diseases. Short-term exposures to high ambient levels of NO_2 may provoke self-limiting symptoms reflecting respiratory illness or irritation in children, but this association is tenuous and inconclusive. Few reliable data exist for assessing the effect on humans of prolonged exposure to high ambient levels of nitrogen dioxide. Studies in children suggest that permanent injury is not a consequence of these exposures, and investigations with various animal models support the likelihood that present levels of NO_2 are innocuous insofar as the respiratory system is concerned. One potentially hazardous effect of NO_2 is the capacity of the pollutant to form carcinogenic nitrosamines in animals tested under highly artificial laboratory conditions. The significance of these observations awaits results from experiments done under realistic conditions. Thus, at present, no definitive evidence exists linking prolonged human exposure to ambient levels of NO_2 to disease, dysfunction or discomfort, and, on the basis of current knowledge, the annual standard of 0.05 ppm of NO_2 is much below the minimum-effects level.

Fifth, billions of dollars are spent annually to limit emissions of NO_2 from automobiles and industrial processes and to control photochemical oxidant pollution. As a result of these efforts, atmospheric levels of air pollution have not worsened and in some areas they have diminished.[98] This improvement in air quality has undoubtedly benefited residents of these areas. Whether these benefits, which primarily affect comfort and athletic ability, justify the present expense or warrant greater or lesser expense is a complex regulatory issue in which Solomon-like decisions are required to ensure the safety and well-being of the populace while at the same time allowing society to benefit from technology.

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Medical Staff Conference

The Ophthalmopathy of Graves' Disease

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs Homer A. Boushey, Associate Professor of Medicine, and David G. Warnock, Associate Professor of Medicine, under the direction of Dr Lloyd H. Smith, Jr, Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

DR SMITH:* *Graves' disease has always intrigued physicians because of its obscure origins and manifold clinical abnormalities. There has been great progress in the field of studying this most common cause of hyperthyroidism—notably better methods of assaying thyroid function and interesting documentation of Graves' disease as seemingly an autoimmune disorder in which the antibody strangely activates rather than impedes a hormonal receptor. Nevertheless, there is much that remains obscure, including the basic mode of action of triiodothyronine itself. Among the areas of residual obscurity is the phenomenon of the ophthalmopathy that is varyingly associated with Graves' disease. For this Medical Staff Conference, this intriguing topic will be explored for us by Basil Rapoport, MD, who is an Associate Professor of Medicine in our department and a member of the Division of Endocrinology at the San Francisco Veterans Administration Medical Center. Dr Rapoport.*

DR RAPOPORT:† Graves' disease is a triad consisting of hyperthyroidism, diffuse goiter and extrathyroidal manifestations including ophthalmopathy and pretibial myxedema. The relationship between the ophthalmopathy and thyroid disease in Graves' disease is not entirely clear, and there is disagreement as to whether or not these two conditions occur independently. When present, the clinical manifestations of Graves' ophthalmopathy can be very distressing, both physically and emotionally. The severity of the condition varies. In some patients ophthalmopathy may be manifest by burning, irritation and photophobia. On physical examination periorbital edema, chemosis (edema of the conjunctivae), conjunctival injection, lid retraction and lid lag may be seen. More severe ophthalmopathy, involving more extensive inflammation and swelling of the retro-orbital tissues, may lead to proptosis and diplopia due to restricted extraocular muscle movement and, at a later stage, fibrosis and retraction of the muscles. When proptosis prevents closure of the eyelids, the cornea is at risk for ulceration and loss of vision. Finally, compression of the optic nerve by the extraocular muscles, particularly in the vicinity of the optic foramen, may lead to loss of vision. There is an excellent recent review on the subject of Graves' ophthalmopathy.[1]

Pathology

The exophthalmos of Graves' disease was initially considered to be due to sympathetic overactivity. In 1944, however, Rundle and Pochin examined the volumes of the orbit and the retro-orbital tissue in Graves' ophthalmopathy[2] and were the first to show that exophthalmos is caused by increased volume of the retro-orbital tissues. In addition, they noted the importance of extraocular muscle involvement in this condition. They observed that the average volume of the bony orbit was 26 ml and that an increase in retro-orbital tissue volume of about 0.7 ml led to a 1-mm increase in protrusion of the globe. The volume of normal extraocular muscles is about 4 ml. Because these muscles may be more than doubled in volume, it is clear how increased volume of the muscles alone can lead to significant exophthalmos.

Some controversy nevertheless persists as to the relative involvement of the different retro-orbital tissues. While earlier studies of gross pathology showed increased volume of retro-orbital fat and of extraocular muscles, more recent studies using computed tomographic (CT) scanning (Figure 1) and ultrasonography have emphasized extraocular muscle involvement to the extent that some physicians now consider the disease to be exclusively a myopathy. Close scrutiny of the evidence suggests, however, that Graves' ophthalmopathy is not specific for muscle, but also involves fat and the lacrimal gland. While this issue is not important clinically, it does influence the direction of studies on the pathogenesis of this disease. It is also interesting that in most cases the extraocular muscles are not involved uniformly; thus, there is a predilection for involvement of the medial and inferior recti. Finally, because the extraocular muscles are frequently thickened at their posterior insertions near the optic nerve foramen, optic nerve compression may occur even without severe exophthalmos.

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ABBREVIATIONS USED IN TEXT

CT = computed tomographic
T_3 = triiodothyronine
TSI = thyroid-stimulating immunoglobulin

Pathogenesis

In the past decade there have been three theories proposed as the basis for the pathogenesis of Graves' ophthalmopathy. First is that thyroid-stimulating hormone (thyrotropin), or a fragment of thyrotropin, binds to specific receptors in retro-orbital tissues, including muscle.[3] Specific immunoglobulins against orbital tissue antigens are postulated to increase the binding of these thyrotropin fragments. Binding of these components is then believed to cause inflammation, swelling and mucopolysaccharide accumulation in the orbit. The attractiveness of this theory has diminished somewhat in recent years because of a lack of supporting evidence. In addition, the hyperthyroidism that is commonly associated with Graves' ophthalmopathy would be expected to suppress secretion of thyrotropin by the anterior pituitary.

A second theory for the pathogenesis of Graves' ophthalmopathy is that extraocular muscles, unlike other muscles, have receptors for thyroglobulin.[4] The interaction between thyroglobulin and its receptors in eye muscle is enhanced by antithyroglobulin antibodies. It is postulated that relatively high concentrations of thyroglobulin reach the orbit via communicating lymphatic channels between the thyroid and the orbit. The adherence of thyroglobulin-antithyroglobulin immune complexes to eye muscle is believed to lead to the binding of lymphocytes via their Fc receptors and subsequent antibody-dependent cellular cytotoxicity. This theory remains attractive, but additional in vitro and in vivo supportive evidence is awaited.

The third proposed pathogenetic mechanism for Graves' ophthalmopathy is that specific antibodies exist for as-yet-undefined antigens in all retro-orbital tissues, predominantly extraocular muscles. Neither thyrotropin, thyrotropin fragments nor thyroglobulin are postulated to be involved in this mechanism. This theory is spurring present attempts to develop monoclonal antibodies against orbital tissue antigens.[5] The possible relationship between cell-mediated immunity and such specific antibodies is uncertain. These studies are currently at an early stage. It is clear, therefore, that unlike the hyperthyroidism of Graves' disease in which thyroid-stimulating immunoglobulin has been implicated as the cause of thyroid overactivity, the mechanism underlying Graves' ophthalmopathy remains much less clearly defined.

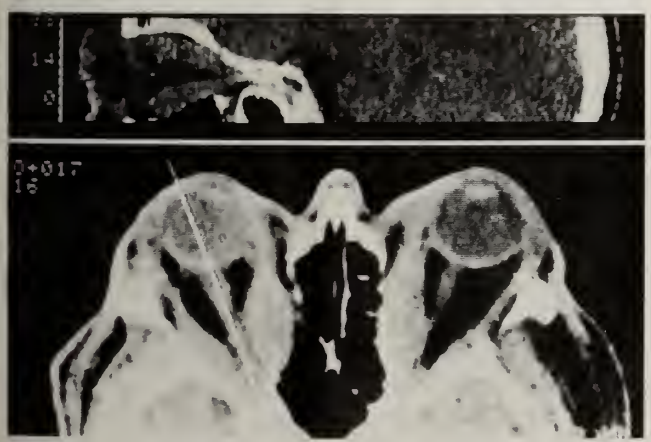

Figure 1.—Computed tomographic scan of the orbit in a case of Graves' ophthalmopathy. **Upper panel,** Sagittal view showing mild thickening of the superior and inferior recti. **Lower panel,** Transverse section indicating extensive thickening of the medial recti. Note the muscle thickening at the apex of the bony orbit that can cause optic nerve compression. (Provided by Francis S. Greenspan, MD, Clinical Professor, Departments of Medicine and Radiology, UCSF.)

Relationship Between Graves' Ophthalmopathy and Thyroid Disease

Considerable interest exists regarding the relationship between ophthalmopathy and hyperthyroidism in Graves' disease. Not surprisingly, because the pathogenesis of the ophthalmopathy is unknown, there is disagreement on this issue. The relationship between ophthalmopathy and hyperthyroidism is of interest for two main reasons. First, the direction of research attempting to understand these conditions is greatly influenced by whether or not these conditions are independent or linked processes. Second, and more important clinically, an association between these two conditions would provide support for those physicians who believe that ablation of the thyroid gland is an important feature in the treatment of ophthalmopathy. The controversy as to whether or not Graves' ophthalmopathy is completely independent of the thyroid component of the disease may be looked at from two viewpoints. The first is whether or not all patients with thyroid disease have concomitant eye disease. The other side of the coin is whether or not isolated ophthalmopathy can exist without clinical or subclinical thyroid disease. The difference between these two aspects tends to be overlooked.

First, focusing on the question of whether all patients with thyroid disease have ophthalmopathy: severe ophthalmopathy occurs in 3% to 5% and detectable ophthalmopathy in 25% to 50% of patients with Graves' disease. In recent years sensitive diagnostic techniques have raised the possibility that all patients with Graves' disease have ophthalmopathy. For example, Werner and co-workers using ultrasonography reported that 44 of 47 (94%) patients with Graves' disease had extraocular muscle thickening.[6] In another study, Forrester and colleagues reported similar data in that all 25 patients with Graves' disease studied had detectable ophthalmopathy on ultrasonography.[7] Using CT scanning, Enzmann and associates found evidence of extraocular muscle involvement in 91% of 116 patients with Graves' disease.[8] When the rise in intraocular pressure is measured on upward gaze, Gamblin and co-workers reported an abnormally large increase in pressure in 61 of 80 (76%) patients with Graves' disease, suggesting that these persons have underlying ophthalmopathy.[9]

These and other studies are presently interpreted by many physicians to indicate that all patients with Graves' disease have ophthalmopathy, even though it may not be clinically evident. However, these data may be somewhat misleading and do not prove the thesis that with increasingly sensitive diagnostic techniques ophthalmopathy will be found in all patients as the patients in these studies were perhaps selected from a population referred primarily for their ophthalmopathy. In addition, as reported in the same studies, the incidence of ophthalmopathy as detected by ultrasonography, CT scanning or increased intraocular pressure is much less in

patients who do not have clinically evident ophthalmopathy. For example, 37% and 60% of patients without clinical evidence of ophthalmopathy had normal ultrasound and CT scans of the orbit, respectively.[7,8] Similarly, in patients with unilateral ophthalmopathy, extraocular muscle thickening in the contralateral eye is only detectable in 50%.[6]

Different types of studies provide perhaps the strongest evidence supporting the thesis that all patients with thyroid disease have ophthalmopathy. Thus Amino and associates have shown in Japan that there is a normal gaussian distribution in the degree of orbital protrusion in Graves' disease (Figure 2).[10] If ophthalmopathy only affected a particular subgroup of patients with Graves' disease, a bimodal distribution would be anticipated. In addition, Gorman has shown a close temporal relationship between the onset of ophthalmopathy and hyperthyroidism.[11]

The second aspect of the relationship between thyroid and eye disease is whether or not "isolated" ophthalmopathy can exist in the absence of thyroid disease. In 1977 Solomon and colleagues identified different subgroups of euthyroid patients with Graves' ophthalmopathy.[12] In support of the findings of a number of previous studies, these investigators noted that ophthalmopathy could occur in some patients without any detectable abnormality in thyroid function as assessed by sophisticated testing. Nevertheless, the concept of isolated ophthalmopathy has been greeted with considerable skepticism by many physicians. Three main lines of evidence have been used against the existence of such a condition. First is that, as discussed previously, there is increasing evidence that all patients with thyroid disease have underlying ophthalmopathy. Second is the presumption that with increasingly sensitive tests for autonomous thyroid function in Graves' disease, all patients with ophthalmopathy will be found to have abnormal thyroid function, albeit subclinical. Third, it has been suggested that some patients with apparently isolated ophthalmopathy have orbital pseudotumor rather than Graves' ophthalmopathy.

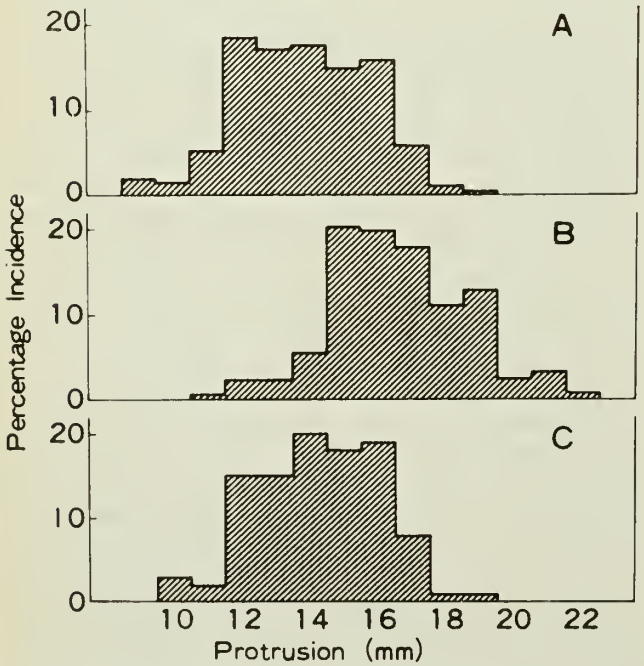

Figure 2.—Frequency distribution of the degrees of protrusion of the eyes in **(A)** healthy subjects, **(B)** patients with Graves' disease and **(C)** those with Hashimoto's thyroiditis. (Reprinted with permission from Amino et al.[10])

The first and last of these arguments cannot be used to refute the thesis that isolated ophthalmopathy does exist. Thus, even assuming that ophthalmopathy does indeed occur in all patients with Graves' disease, it does not follow logically that "isolated" ophthalmopathy is not a distinct condition. It is the other side of the coin, namely, whether or not thyroid disease occurs in all patients with ophthalmopathy, that will determine the answer to this question. The argument that isolated Graves' ophthalmopathy is in fact orbital pseudotumor is similarly unconvincing because there is significant overlap between these two conditions and it may be difficult to distinguish between them.

The present concept is that unilateral Graves' ophthalmopathy and orbital pseudotumor are separate diseases that are clearly distinguishable on CT scanning.[13] The diagnosis of Graves' ophthalmopathy on CT scan is based on swelling primarily restricted to the extraocular muscles. Conversely, infiltration largely separate from the extraocular muscles is considered to be pseudotumor. However, the difference between these two conditions may not be so clear-cut. For example, orbital pseudotumor has been reported to occur in cases of Graves' disease (Table 1).[14,15] We have also recently seen such a case. This association confuses the distinction between Graves' ophthalmopathy and pseudotumor because the latter is a diagnosis of exclusion.[16] That is, a diagnosis of pseudotumor requires the exclusion of endocrine exophthalmos (Graves' disease) and other conditions such as orbital tumors and granulomatous or vascular space-occupying lesions. Orbital pseudotumor may also be bilateral. Indeed, in the series of Enzmann and colleagues, six of nine patients with orbital pseudotumor had bilateral involvement.[13] The histologic features of orbital pseudotumor and Graves' ophthalmopathy are similar, with both showing inflammation with lymphocytic infiltration and fibrosis. It is also known that extraocular muscle thickening may be seen in pseudotumor of the orbit. Finally, both pseudotumor and Graves' ophthalmopathy respond to the same types of therapy, as discussed below. Evidence that these two conditions are in fact different is that orbital pseudotumor is occasionally associated with fibrosis in other parts of the body, such as the retroperitoneum. In contrast, retroperitoneal fibrosis is not a described feature in cases of Graves' ophthalmopathy. Whether or not pseudotumor of the orbit and Graves' ophthalmopathy are separate conditions, therefore, remains the subject of a heated debate.[14,15]

Diagnosis

In most cases of bilateral ophthalmopathy, there is a present or past history of thyroid dysfunction, and further tests are unnecessary to establish a diagnosis of Graves' ophthalmopathy. However, when thyroid function appears to be normal it may be necessary to do additional tests to determine whether or not the ophthalmopathy is related to Graves' disease. The presence in serum of thyroglobulin or microsomal antibodies suggests underlying autoimmune thyroid disease (Hashimoto's thyroiditis) and supports a diagnosis of Graves' ophthalmopathy. The thyrotropin-releasing hormone stimulation test and the triiodothyronine (T_3) suppres-

TABLE 1.—*Orbital Pseudotumor*

May occur in cases of Graves' disease
Frequently bilateral
Histology similar to that in Graves' ophthalmopathy (lymphocytic infiltration and fibrosis)
Diagnosis on CT scan assumes Graves' ophthalmopathy is restricted to eye muscles
Extraocular muscle thickening may be present
Cases respond to the same therapy as for Graves' ophthalmopathy

CT = computed tomographic

TABLE 2.—*Graves' Ophthalmopathy—Approach to Therapy*

Is the patient euthyroid?
Is the disease in an evolving or a stable phase?
Is there a threat to vision?
Optic nerve compression
Corneal exposure
What is the patient's psychological response?

sion test (determining whether T_3 administration will decrease the thyroid radioactive iodine uptake by at least 50%) are not generally indicated for this purpose. The thyrotropin-releasing hormone test determines whether or not clinical or subclinical hyperthyroidism is present. However, a normal thyrotropin response to thyrotropin-releasing hormone (indicating euthyroidism) does not exclude the presence of thyroid autonomous function, particularly if there is concurrent Hashimoto's thyroiditis. The T_3 suppression test is time consuming and expensive. A simpler test for determining the presence of thyroid autonomy is the measurement of thyroid-stimulating immunoglobulin (TSI) levels in serum.[17] Even though the presence of TSI correlates better with thyroid disease than with ophthalmopathy, TSI is a specific autoantibody in Graves' disease and its detection helps establish guilt by association, namely, a diagnosis of Graves' ophthalmopathy. If any question remains about the diagnosis, particularly in unilateral euthyroid ophthalmopathy in which the presence of other orbital pathology cannot be excluded, an orbital CT scan is valuable. However, this should not be done as a routine diagnostic procedure.

Therapy for Graves' Ophthalmopathy

Four issues should be considered in treating patients with Graves' disease (Table 2). First, is the patient euthyroid? Although there are no definitive data as to the influence of hyperthyroidism or hypothyroidism on the ophthalmopathy of Graves' disease, it is the general clinical consensus that progression of the disease is slowest when a patient is euthyroid. Therapy for either hyperthyroidism or hypothyroidism should be initiated with the goal of attaining euthyroidism within a relatively short period of time. A second consideration in therapy is whether the disease is in an evolving or a stable phase. The natural course of Graves' ophthalmopathy is an initially rapid onset over a period of a few weeks, followed by plateauing of the severity of the manifestations of the disease. The pathology differs during these two stages and thereby influences the therapeutic approach. The progressive phase is associated with acute inflammatory and edematous changes in the retro-orbital tissues. Once the condition has been stable for 6 to 12 months, there is a greater degree of fibrosis, particularly of the extraocular muscles. A third factor influencing therapy is whether or not there is a threat to vision. Decreased visual acuity may be due to optic nerve compression or corneal exposure. Clearly, in this situation treatment is urgent and a more drastic form of therapy is indicated. Fourth and finally, it is important to understand a patient's psychological response to his or her condition. Young women are more likely to be psychologically affected by relatively mild ophthalmopathy than, for example, older men. Because the therapy for Graves' disease involves either minor, symptomatic treatment or major therapy with significant side effects, with very few options in between, it is prudent to avoid major therapy if the condition is stable, vision is not threatened and the patient is not psychologically disturbed by the condition. Conversely, the threshold of intervention with major therapy will be lower in more psychologically affected persons.

During the evolving phase of ophthalmopathy, chemosis and conjunctival irritation can be treated by elevating the head of the bed 10 to 15 cm (4 to 6 in)—such as by using bricks—and by using artificial tears (0.5% methylcellulose drops). If proptosis prevents complete closure of the eyes during sleep, paper tape can be used to keep the eyelids shut. Diuretics have been used to treat chemosis, but there is little evidence that this therapy is effective. Along with the symptomatic treatment just discussed, it is necessary to initiate therapy to correct the underlying hyperthyroidism or hypothyroidism.

A more aggressive approach is required if the proptosis worsens, or if there is an onset of diplopia or optic nerve compression. An initial form of therapy under these circumstances is supervoltage irradiation to the orbit.[18] This radiation (2,000 rads over a two-week period) can be highly focused to avoid the cornea. Under some circumstances, systemic glucocorticoid therapy can be added to this regimen, or substituted for the orbital irradiation.[19,20] I would add prednisone, 60 mg a day, if progressive ophthalmopathy is not responding to orbital irradiation, or if the condition is particularly severe, and especially if it is associated with decreasing visual acuity. In adolescence, prednisone should be given without initially trying orbital irradiation. This is because the long-term effects of this form of therapy are as yet uncertain. The goal with the use of high-dose glucocorticoid therapy is to taper the dose as rapidly as possible after achieving the maximum effect. In some patients a course of a few weeks is sufficient to produce pronounced improvement, and the prednisone dosage may then be tapered without subsequent problems. However, in other patients the ophthalmopathy may flare as the prednisone dose is reduced and this leads to a clinical dilemma common to many other diseases in which prednisone is administered, namely, difficulty in weaning a patient off the drug. In a few unfortunate patients, orbital irradiation and prednisone are not sufficient to prevent deterioration of vision related to optic nerve compression or corneal exposure due to severe proptosis. Under these circumstances, surgical decompression of the orbit should be done.[21] The most commonly used procedure at present involves removing part of the antral and ethmoid walls of the bony orbit.

During the stable phase of Graves' ophthalmopathy, a surgical procedure is valuable in improving the cosmetic appearance of a patient. Relatively minor operations such as

Mueller muscle resection and levator recession, or the insertion of scleral grafts, can be done to correct eyelid retraction. Mild diplopia can be treated optically using prismatic lenses. Attempts to correct the diplopia surgically should only be made during the stable phase of the disease. It is during the stable phase of ophthalmopathy that orbital decompression for severe exophthalmos is most successful. This procedure should only be done if the proptosis is causing severe emotional problems or if there is continued corneal exposure. Extraocular muscle recession should not be done before orbital decompression because the latter procedure may result in extraocular muscle imbalance that then requires further surgical therapy.

A number of unproved or experimental therapeutic modalities have been used for the treatment of Graves' ophthalmopathy. Perhaps most controversial of these is total ablation of the thyroid gland, either surgically or by the use of iodine I 131. Most studies have found total thyroid ablation to be ineffective. Even in the study of Gwinup and co-workers, one of the few to conclude that this therapy is beneficial,[22] the extent of improvement in the exophthalmos was fairly minimal. Radioiodine therapy may also produce an exacerbation in the ophthalmopathy of Graves' disease, either clinically apparent or evident on ultrasonography. It should also be noted that Graves' ophthalmopathy can occur even after total thyroid ablation, and occasionally occurs even in the absence of underlying thyroid disease. At present, therefore, there is little evidence that total thyroid ablation is beneficial in this condition.

There have been a number of recent reports on the use of a variety of immunosuppressive drugs in cases of Graves' ophthalmopathy,[23-25] including cyclophosphamide, azathioprine and cyclosporine. Much more experience with these drugs is necessary before they can be used in Graves' ophthalmopathy, particularly because of their significant side effects. Finally, plasmapheresis has been reported to be effective in a few patients with this disease.[26,27] This is an expensive form of therapy, however, and requires the concomitant use of immunosuppressive drugs. These types of therapy should therefore not be considered except perhaps in a rare case of severe disease that does not respond to conventional therapy.

In conclusion, our understanding of the pathogenesis of the ophthalmopathy of Graves' disease lags behind that of the thyroid component of this condition. Similarly, the therapy for Graves' ophthalmopathy is not as effective as that for hyperthyroidism. The approach to a patient with ophthalmopathy should be multidisciplinary, involving the physician, an ophthalmologist and occasionally a surgeon or a radiotherapist. The psychiatric aspect of this condition should also not be underestimated. Perhaps the most difficult patients to treat are those whose disease is of intermediate severity—that is, not severe enough to clearly justify the use of major forms of therapy. These patients require much support, and good rapport between doctor and patient is important in order to decide at which stage to proceed with major therapy.

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Epitomes
Important Advances in Clinical Medicine

General Surgery

The Scientific Board of the California Medical Association presents the following inventory of items of progress in general surgery. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, research workers or scholars to stay abreast of these items of progress in general surgery that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on General Surgery of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to Division of Scientific and Educational Activities, California Medical Association, 44 Gough Street, San Francisco, CA 94103

Arm Veins—Durable Autogenous Alternatives for Arterial Bypass

THE CEPHALIC and basilic arm veins, by virtue of their length, diameter and patency, are satisfactory substitutes for the saphenous vein in leg bypass operations. Although frequently gossamer thin, the bursting strength of arm veins exceeds 400 mm of mercury; their diameters average 5 to 7 mm and they are more uniform in caliber than their saphenous counterparts. The medially placed basilic vein spans the common femoral to the infrageniculate popliteal artery segment; the cephalic vein, when excised completely from the wrist to the deltopectoral groove, extends to the tibial vessels. Most important of all, arm veins are endothelialized, compliant and autogenous.

The test of any graft material is patency and it is here that arm veins show their desirability. The gold standard for graft patency and effectiveness is the reversed saphenous vein. Neither Dacron, polytetrafluoroethylene, human umbilical vein nor endarterectomy or balloon angioplasty has approached the long-term durability of autogenous vein. The tantalizing impulse to "go to the shelf" for a synthetic graft in the 20% to 40% of patients with an inadequate or previously excised saphenous vein should be tempered by the disappointing patency rates of nonautogenous conduits.

A recent comprehensive follow-up of arm vein grafts to the popliteal and infrapopliteal arteries has shown short- and long-term patency equivalent to that of saphenous veins. Limb salvage was the indication for 55% of the 70 operations. No in-hospital mortality was observed and fears of donor upper extremity morbidity were unfounded. Complications such as inflow and outflow occlusion and neointimal proliferation occurred infrequently and were managed as with saphenous grafts. Late aneurysmal dilatation, reported by others, occurred only once.

With so many desirable features, it is perplexing why the use of arm veins for arterial grafts has not achieved widespread popularity and application. Learning to excise and prepare these delicate vessels and to do anastomoses can be frustrating and demands patience and technique. Magnification is advisable. With a two-team approach, the operating time is about 20 minutes longer than that for a saphenous vein bypass. A successful outcome with arm vein grafts requires educating patients, surgeons, phlebotomists and vein-care teams, referring physicians and nursing personnel.

A secondary surgical procedure for graft failure does not mandate the use of a synthetic graft. In this situation, arm veins have also yielded better long-term patency than any synthetic graft. Unfortunately, some patients by this time will no longer have a satisfactory undamaged arm vein and should properly receive a synthetic conduit. Nevertheless, the advantages of autogenous grafts dictate that contemporary vascular surgeons be prepared to use arm veins as bypass grafts and to include them in their therapeutic armamentarium.

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Needle Aspiration of the Thyroid Gland

A PRECISE DIAGNOSIS and therapy for thyroid nodules and certain other thyroid abnormalities, such as chronic lymphocytic thyroiditis, require histologic identification. Although some physicians retain reservations, increasing evidence indicates that needle biopsy best provides this information in selecting patients for surgical and medical treatment of thyroid nodules.

Three major techniques are used for needle biopsy of the thyroid gland. Experience leads to individual preferences and the efficacy of different techniques remains somewhat controversial. Tissue that is representative of the thyroid abnormality must be obtained. *Fine-needle aspiration biopsy* can be used in nearly all situations, is best accepted by patients, has high reliability in experienced hands and is gaining in popularity. This technique requires a knowledgeable cytologist. *Large-needle aspirates* provide cellular material for *histologic* study. Experience indicates that the results of this procedure are less dependable than those from fine-needle aspiration. *Core needle biopsy* (usually with a Silverman or a TruCut needle) provides tissue for histologic study. For the latter technique, the thyroid nodule should be more than 2 cm in diameter (1.5 cm if easily accessible). This requires a small skin incision, is a slightly more complicated procedure than fine-needle aspiration and is less acceptable to patients. Core needle biopsy is highly (90%) reliable and appears to be most useful in cases that remain a diagnostic problem after fine-needle aspiration biopsy; as such, it is decisive in 15% to 20% of cases of thyroid nodules.

Fine-needle aspiration biopsy permits immediate assessment of virtually all thyroid nodules and is our preferred basic technique. Strict criteria for the adequacy of specimens are mandatory, with the presence of clumps of normal cells in at least two slides required to permit a report of a benign lesion with the fine-needle technique. Aspirates are obtained from at least six different locations of the nodule. We classify results as benign, inadequate, indeterminate and malignant, with appropriate characterizations for each category.

Cystic degenerating thyroid nodules commonly result in an inadequate specimen from needle biopsy. Biopsy by fine-needle aspiration or core needle biopsy of the solid component of such lesions following aspiration of fluid may produce an adequate specimen.

Indeterminate specimens from needle biopsy usually indicate a cellular lesion that cannot be identified as either a benign cellular adenoma or low-grade follicular carcinoma of the thyroid gland. For this and similar difficulties, including Hürthle cell lesions, core needle biopsy provides clarification in some cases.

The results of fine needle biopsy of the thyroid gland can be summarized as follows:

False-negative	2% to 4%
False-positive	0% to 3%
Inadequate	3% to 11%
Indeterminate	17% to 30%
Carcinoma in indeterminate cases	20% to 60%

Complications from fine-needle aspiration biopsy are negligible and consist primarily of minor bleeding. Injury to adjacent structures and more serious bleeding rarely occur after the use of larger needles. The frequency of these complications is related to the skill and experience of a physician and the location of a lesion. Seeding of neoplastic cells has been reported to be extremely rare and restricted to the use of large needles.

Needle biopsy is cost effective compared with other diagnostic studies and management plans for thyroid nodules. Its capacity for selectivity of treatment frequently results in twice the frequency of thyroid carcinoma in patients undergoing surgical procedures for thyroid nodules in practices using needle biopsy compared with previous experience when the procedure was not utilized.

Needle biopsy of the thyroid gland must be used as only one important tool. An operation is recommended for cases in which the study results are positive, indeterminate or inadequate with other factors supporting a surgical procedure, and for cases of large benign solid thyroid nodules. Needle biopsy findings are significant in preoperative discussions with patients and in directing the extent of the operative procedure. For benign cases, medical follow-up and periodic repeat biopsy are justified.

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Use of Computed Tomography in Cases of Blunt Abdominal Trauma

THERE HAS ALWAYS been a need for a sensitive discriminating means of diagnosing intraperitoneal and retroperitoneal injury following blunt trauma. The primary need for such a diagnostic test is to avoid missing an injury, which can often be fatal or result in serious disability. This is particularly true in a shocked or unconscious patient. A secondary need is to avoid laparotomy if there is minor, insignificant or absence of injury. It is far better to err on the side of laparotomy than not, however. I know of no patient who died from diagnostic laparotomy for blunt trauma, but I do know of several instances wherein a patient died because laparotomy was not done.

For the past 15 years, the mainstay of diagnosis in a stable trauma patient with a possible abdominal injury has been peritoneal lavage. It is relatively easy to do and is fairly specific and sensitive. Its disadvantages are that it does not identify retroperitoneal injuries and, in some instances, it may be too sensitive. For example, the results may be "positive" with relatively minor liver injuries. Nevertheless, peritoneal lavage is still widely used and is still the diagnostic study of choice in many centers.

Computed tomography (CT) has advantages over peritoneal lavage in that it is both qualitative and quantitative. CT shows specific organ injury and quantitates relative blood loss, thus allowing a surgeon to use judgment on the need for laparotomy. In addition, CT is capable of diagnosing retroperitoneal injuries, specifically those involving the pancreas, duodenum and kidneys. Injuries to the diaphragm, small bowel and colon can be detected by both CT and peritoneal lavage, but both tests can also miss these injuries.

There are certain caveats and disadvantages with CT. Optimally, CT of the abdomen for blunt trauma should be done with a relatively recent generation CT scanner because of the

improved resolution. In addition, double contrast, with media given by mouth and by vein, will enhance diagnosis. Interpretation requires a senior radiologist; in our institution, the radiology residents and surgeons miss 15% of injuries. CT should *not* be done on an unstable trauma patient. Like peritoneal lavage, CT should not be overused or abused. It should not be done in a case of obvious blunt abdominal trauma nor as a substitute for a thorough clinical examination by a general surgeon. Finally, CT may be slightly more expensive than peritoneal lavage, but because of the oversensitivity of peritoneal lavage, this is probably offset by reducing the need for laparotomy.

In summary, CT represents a new diagnostic method for evaluating intraperitoneal and retroperitoneal injuries. It is both specific and sensitive. I anticipate the introduction of newer imaging modalities in the near future for evaluating cases of blunt abdominal trauma. For the present, however, CT represents the state of the art.

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Liver Transplantation

THE FIRST human liver transplant was carried out by Thomas Starzl, MD, in 1963. The initial liver transplant procedures done on the West Coast were done in the late 1960s at University of California medical centers by Fonkalsrud at Los Angeles and DeLorimier at San Francisco. Following these initial transplantation efforts, interest waned in the procedure. Throughout the 1970s, the world's experience in liver transplantation was limited to the isolated efforts of Starzl in the United States and Calne in England.

Since the advent of cyclosporine, considerable interest has been generated in liver transplantation. Active liver transplantation programs exist in at least 11 centers in the US, and a similar number in Europe and Asia. In the West, active liver transplant programs now exist at the University of California, Davis, in Sacramento, at UCLA and in Phoenix.

One-year patient survival rates in the precyclosporine era were from 30% to 40%. Since the advent of cyclosporine, one-year patient survival rates of between 50% and 75% have been reported. At present, the highest survival rate occurs in the pediatric population in which biliary atresia is the most common indication. It is now clear that mortality is also related to the degree of hepatic, renal and pulmonary failure present at the time of transplantation.

The most common indications for hepatic transplantation in adults include nonalcoholic cirrhosis, primary liver cancer, primary biliary cirrhosis and sclerosing cholangitis. Common indications in children include biliary atresia, α_1-antitrypsin deficiency and inborn errors of metabolism. At present, the guidelines for the timing of hepatic transplantation are poorly defined and vary widely depending on an individual patient and the diagnosis.

The resources and institutional support required for a successful liver transplantation program are considerable. An institution that initiates a liver transplant program must make a major commitment to its support. In addition, liver transplant programs must have physicians who are experienced in hepatic transplantation and who are expert in the fields of hepatology, pediatrics, intensive care, infectious disease, pathology, anesthesiology and immunology. Of particular importance is the role of the blood bank and the availability of social and psychiatric services.

Hepatic transplantation programs should be initiated under the guidance of a supervisory committee consisting of both medical and lay persons with expertise in the fields of hepatology, transplantation and ethics. This committee should review each candidate before transplantation and also review the quality of health care delivery.

Funding resources have been a continuing problem in liver transplantation. The estimated cost of a liver transplantation and initial hospital care is approximately $125,000, with an estimated cost of $25,000 a year after the initial hospital admission.

Liver transplantation represents a viable new means for treating patients with end-stage liver disease. For the foreseeable future, liver transplantation efforts will be limited to a small number of institutions that are willing to meet the tremendous resource commitment that is required to achieve optimal success levels. As limited numbers of hepatic transplantation programs will exist, patients will continue to be referred from a large geographic area, and local physicians will continue to become increasingly involved in their preoperative and postoperative care.

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Surgical Treatment of Morbid Obesity

MORBID OBESITY is a disease that leads to many other diseases associated with a compromised way of life, longevity and mortality. There is no drug therapy or medical regimen that is recognized as a standard therapy for its successful treatment. The surgical procedures presently in vogue involve reducing or restricting the gastric reservoir. Intestinal bypass has proved unsatisfactory because of its long-term failure rate and high association of untoward side effects. Various stapling techniques have evolved over the past ten years in an effort to provide an easy, satisfactory technique that will be permanent. Stapling the stomach into a small reservoir with a controlled outflow has been the aim. Success rates have been reported at higher than 85%. A long-term slow regain of weight in some patients undergoing staple procedures has been recognized. This has been due to some enlargement of the reservoir, the outlet of the stomach or pulling out of the staples.

The search for a simple, permanent surgical technique continues. Various banding techniques, with and without the use of staples, are being proposed because of dissatisfaction

with the late weight gain in stapled patients. A procedure of gastric wrapping and placing of a nonabsorbable, permanent restricting sleeve around the stomach appears to have some advantages. The stomach is not penetrated, or sutured, thereby diminishing some of the early morbidities sometimes seen with the more invasive gastric techniques. The procedure is permanent and not associated with late weight gain.

With the gastric-reduction procedures, there do not appear to be the metabolic side effects that so often attended the earlier intestinal bypass procedures.

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Limb Salvage for Soft Tissue Sarcoma of the Extremities

SOFT TISSUE sarcomas of the extremities are unusual malignant tumors. Fewer than 4,000 cases of such tumors are treated annually in the United States. Amputation has been the standard therapy. In theory, amputation should be done one joint above the anatomic region involved by the sarcoma. In practice, however, even radical amputations such as hemipelvectomy or intrascapular thoracic amputation for large proximal lesions often result in close margins. Despite these radical amputations, the local recurrence rate can be as high as 10% with amputation alone.

Early attempts to surgically treat cases of soft tissue sarcoma by less than amputation resulted in high local failure rates. Local excision or enucleation of a tumor invariably cut through microscopic areas of disease. Soft tissue sarcoma appears grossly to be encapsulated. However, this "pseudocapsule" is composed of compressed normal tissue infiltrated by malignant cells. The enucleation or local excision leaves viable tumor cells in situ and will almost always lead to local recurrence.

Excision or compartmental resection can be successful in treating some patients with soft tissue sarcoma in an extremity. The theory of compartmental resection is to remove the entire involved muscle compartment from origin to insertion. In practice, this is often difficult because sarcomas are rarely confined to one muscle group. Most tumors cross several fascial planes and the tumor's site of origin remains obscure. Wide excision removes the tumor and a rim of normal tissue in an attempt to avoid transection of microscopic disease. Local recurrence after wide excision or compartmental resection may be as high as from 30% to 40%.

The development of radiotherapy has resulted in successful alternatives to amputation. Irradiation alone is inadequate to treat gross disease and must be combined with surgical resection to avoid dose-related complications or local recurrence. Irradiation is more likely to be effective when no gross disease remains. Resection of the tumor and postoperative radiotherapy are extremely successful for sarcomas located distal to the elbow or knee. Large, more proximal tumors cannot usually be successfully treated with resection and radiotherapy.

The addition of chemotherapy to the management of a primary tumor on an extremity has achieved local control rates at least as low as those of radical amputation. We infuse doxorubicin hydrochloride intraarterially because it is a known irradiation sensitizer. After three days of chemotherapy (total dose, 90 mg) a patient receives 3,500 rads of radiotherapy preoperatively over ten days. This rapid fractionation of radiotherapy results in few complications and is biologically equivalent to 5,000 rads. The tumor is then excised with a rim of surrounding normal tissue, liberally using frozen sections for confirmation of tumor-free margins. Wherever tumor abuts against bone, blood vessels or nerves, the respective periosteum, adventitia or perineurium is removed with the operative specimen.

Using this technique, 225 patients with soft tissue sarcoma of an extremity have been treated with a local control rate of greater than 94%. Serious complications requiring reoperation were uncommon and may be related to the dose of irradiation. Amputation is no longer the only method of therapy for soft tissue sarcoma of an extremity. Patients with soft tissue sarcomas of an extremity can be treated with a limb-preserving, multimodality approach that affords a higher local control rate than a surgical procedure alone and preserves a viable, functional extremity in 94% of cases. Additionally, survival is equivalent to that achieved with radical amputation.

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Ex Vivo Renal Artery Reconstruction

THIS YEAR RENAL FAILURE will develop in 15,000 persons, who will then require hemodialysis. With the increasing burden of hemodialysis, there is an impetus to develop new surgical techniques to revascularize kidneys affected by complex renovascular lesions. To salvage these kidneys and maintain renal function, conventional in situ methods are not appropriate, but ex vivo repair, a new technique, permits precise microvascular repair and avoids nephrectomy. "Bench work" surgical intervention describes the sequence of temporary nephrectomy, ex vivo renal perfusion and microvascular repair.

Many indications exist for an ex vivo repair. The most common is the reconstruction of lesions that affect the primary and secondary branch of the renal arteries. The most common cause of these distal lesions is fibromuscular dysplasia. Atherosclerotic renal artery aneurysms occur at this location in the renal artery as well. Additionally, several renal arteries in a donor kidney may require an ex vivo microvascular repair before transplantation. Less frequent indications include excision of bilateral renal parenchymal tumors or a tumor in a solitary kidney, repair of renal or ureteral injuries, removal of multiple or staghorn calculi and repair of a prior renal artery reconstruction that has failed.

The kidney is approached through either a midline or a flank incision with circumferential dissection of the renal artery and vein. After they are transected, the kidney is removed from the renal fossa and placed on continuous hypothermic perfusion on a dissecting platform. A reconstruction procedure can then be done in an asanguineous field, with optimal exposure and illumination, using microvascular surgical technique. Following repair, the kidney can be replaced in either an orthotopic or a heterotopic position in the iliac fossa. Although an autogenous saphenous vein is an acceptable graft for renal artery substitution, we prefer the branched hypogastric artery because of its anatomic configuration and size, its resistance to aneurysmal degeneration or stricture and its growth when implanted in a growing child.

Although most of the surgical literature on this subject comprises case reports, we have followed for periods of six months to six years 26 patients who underwent ex vivo repairs. Of 23 reconstructions, 22 were patent as determined by postoperative angiography. In all, 95% of the hypertensive patients were cured or their conditions improved during follow-up. Late postoperative arteriograms (more than three years) showed continuing patency in all six patients studied.

The ex vivo "bench work" operation, a relatively recent addition to vascular surgical procedures, has, by preserving kidneys and their important function, provided a significant contribution for patients affected with a variety of complex lesions.

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Preoperative Biliary Tract Drainage

DURING THE 1970S, numerous authors reported that percutaneous transhepatic drainage could be done with little morbidity. During this same period, surgical relief of obstruction in severely jaundiced patients was associated with postoperative morbidity in 40% to 60% and mortality in 15% to 25% of patients. For this reason, preoperative percutaneous transhepatic drainage has been recommended for these patients. Moreover, two retrospective studies from Japan and another nonrandomized analysis from Ohio State University suggested that preoperative biliary tract drainage might be helpful. Thus, on the basis of these retrospective studies, many clinicians have accepted that preoperative biliary drainage should be done routinely before surgical intervention in patients with deep jaundice. However, more recent reports from several institutions have cautioned that a significant proportion of patients undergoing this procedure are subject to both early and late complications.

Thus, controversy exists as to what role preoperative biliary drainage should play. To help answer this question, three prospective randomized studies have recently been completed. The first such study was done by Hatfield and associates from South Africa. These investigators failed to find any advantage in terms of decreased postoperative morbidity or mortality for preoperative percutaneous transhepatic drainage: 4 of 29 patients (14%) who had drainage and 4 of 28 (14%) who did not undergo drainage died. Five of the eight deaths, however, occurred in patients in whom either percutaneous transhepatic drainage could not be done (one patient) or who did not have a surgical procedure (five patients). The second study was done at the Hammersmith Hospital in London by McPherson and co-workers. In this study, of 65 patients, hospital mortality was actually higher in the drained (32%) than in the undrained (19%) patients ($P > .05$). Of 11 deaths in the drained group in this study, 5 occurred in patients who did not have an operation.

The third study was done at the UCLA Medical Center. In this study of 75 patients, hospital mortality was 8% among drained patients and only 5% in those patients who had surgical treatment without preoperative percutaneous transhepatic drainage. In both this study and the Hammersmith study, no significant differences in postoperative morbidity were noted between the drained and undrained patients. Moreover, in both of these studies the duration of hospital stay was significantly prolonged ($P < .05$) in the patients who had preoperative biliary tract drainage. Thus, although retrospective analyses suggested that preoperative percutaneous transhepatic drainage might be beneficial, prospective studies have not supported this early enthusiasm. One criticism of each of these prospective studies, however, is that the duration of preoperative drainage (10 to 18 days) may not have been sufficient to reverse the multiple metabolic and immunologic abnormalities associated with severe obstructive jaundice.

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Percutaneous Abscess Drainage and Related Radiologic Procedures

PERCUTANEOUS DRAINAGE PROCEDURES continue to evolve with new and innovative advances. Abscesses that previously were not considered appropriate for catheter drainage may be cured in some cases, while needle puncture of certain fluid collections and organs that had been assiduously avoided now is done safely and with clinical benefit. Progress has accrued from laboratory work, improvement in techniques and the necessity of application in desperately ill patients with no reasonable alternatives.

Unilocular (or bilocular) and relatively superficial abscesses are drained with catheters successfully in about 90% of cases. Because of superior resolution, computed tomography (CT) is used for guidance in most cases. The use of large, multihole sump systems, an adequate number of catheters and copious irrigation has now made this a routine procedure. Some hepatic abscesses, those in superficial abdominal

sites, and abscesses in extremities (such as in the thigh) are drained under sonographic guidance.

Enteric-related abscesses have been drained successfully or reduced by partial drainage. Thus, appendiceal abscesses, peridiverticular abscesses, Crohn's-related abscesses and perianastomotic abscesses are amenable to percutaneous abscess drainage. Cutaneous fistula formation after catheter drainage of Crohn's disease abscesses has not been reported to date. The goal of percutaneous treatment for periappendiceal abscesses is to allow a patient's condition to "cool down" and thus to simplify the surgeon's task at a subsequent appendectomy. With enteric-related abscesses, longer term catheterization (several weeks) is often required, compared with unilocular uncomplicated abscesses (about five to ten days).

Patients with pancreatic abscesses and pancreatic pseudocysts have been treated successfully in some cases and improved in other cases. Failure of percutaneous drainage generally occurs when too few catheters are placed or they are removed too quickly. For successful pseudocyst drainage, the communication to the disrupted pancreatic duct must seal, and antegrade obstruction of the duct must resolve. Transgastric placement of catheters for percutaneous drainage has been advocated by some. Successful pancreatic abscess drainage usually requires more than one catheter because the collections are frequently multiloculated; similarly, more follow-up studies (sinography, sonography and CT) are utilized for close follow-up and additional catheter maneuvering, if necessary. These are tedious, prolonged drainages but are frequently helpful in critically ill patients.

Amebic abscesses are drained in a minority of cases. Specific indications for percutaneous abscess drainage include the following: to differentiate pyogenic from amebic in an acute situation, clinical deterioration while receiving medication, initial false-negative serology, pain and imminent rupture and left lobe abscesses. Ultrasound may be used for guidance in some of these cases.

Collections in the chest that are not drained successfully by standard tube thoracostomy due to tube malpositioning may be drained by CT- or ultrasound-guided percutaneous drainage. Some of the most dramatic cures of purulent collections are achieved with catheter drainage of empyemas or infected pericardial collections. When lung abscesses do not have adequate bronchial drainage, they too may be drained by percutaneous catheters. These catheters are preferentially inserted through areas of previous pleural contamination, so as not to spread infection to uninvolved pleura.

Drainage of hematomas, lymphoceles and benign cysts has also been accomplished percutaneously. Each of these is complicated by various specific problems: hematomas are quite thick, lymphoceles tend to recur due to leakage of small lymphatics and cysts may recur due to persistent mucosal secretion. The last may be sclerosed in some cases through the percutaneous catheters.

Percutaneous radiologic-guided puncture of the stomach for feeding or decompression is an outgrowth of percutaneous drainage techniques. It is done under fluoroscopy, with preprocedure location of the transverse colon and sonographic identification of the left lobe of the liver to avoid inadvertent puncture. Catheters are placed directly into the stomach after insertion of a nasogastric tube and inflation of the stomach with either an intragastric balloon, fluid or air. Catheters may be placed either into the stomach or through the stomach into the small bowel for more distal feeding or decompression.

Percutaneous puncture of the gallbladder is used for biliary tract decompression for malignant obstruction, temporizing cholecystostomy for cholecystitis and empyema of the gallbladder or as an access for stone removal. *Echinococcus* cysts, once considered taboo to puncture, have now been reported to have undergone successful percutaneous drainage. The *Echinococcus multilocularis* cyst apparently can be punctured safely, whereas the *Echinococcus alveolaris* type has associated anaphylactic risk.

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Anal Sphincter-Saving Operations

SELECTED CASES of rectal cancer, chronic ulcerative colitis and colonic polyposis may be treated today with sphincter-preserving operations. In the past, many of these patients would have had complete excision of the rectum with a permanent ileostomy or colostomy. Enthusiasm and interest in new techniques for sphincter preservation arise from a better understanding of the various diseases, an improved appreciation of sphincter physiology and the continued desire of patients and physicians to preserve sphincter function, thereby avoiding a permanent stoma.

Rectal cancer involving the upper third of the rectum is conventionally treated with a low anterior resection with anastomosis. However, tumors involving the middle and lower thirds of the rectum have more often been treated by abdominoperineal excision of the rectum. Extended low anterior resection is today done for many of these tumors in the lower rectum provided an adequate margin distal to the tumor can be obtained (2 to 5 cm). Wide excision of the surrounding tissues and retrorectal lymphatics is important to achieve local control.

The development of new intraluminal stapling devices has aided technically in carrying out low rectal anastomosis or coloanal anastomosis done transanally. A temporary diverting colostomy may accompany these low restorative resections to protect the patient if an anastomotic leak should occur. In addition, cancers involving the lower third of the rectum may be selectively approached transanally by excising locally or fulgurating. Criteria for this approach include tumors that are exophytic, well differentiated, mobile and of relatively small size. Caution in these approaches must be stressed in order not to sacrifice principles of adequate cancer surgical treatment, thereby risking local recurrence. To date, results of sphincter-saving procedures for rectal cancer that include

wide excisional pelvic dissection and intraluminal washout appear to compare favorably with those of total rectal excision.

Severe inflammatory changes (chronic ulcerative colitis) or extensive polyposis of the rectum (familial polyposis) often preclude an ileorectostomy after removing the abdominal colon. Because both diseases involve only the mucosa of bowel (compared with Crohn's transmural disease), recent trends include removing or stripping the mucosa of the rectum, leaving the muscular tube of bowel with intact nerves—thereby preserving the sphincter. Mucosal stripping of the rectum is done by entering the submucosal plane at the anorectal junction and removing mucosa of the lower rectum. Following abdominal colectomy, a pouch of terminal ileum is constructed to allow distensibility and reservoir capacity. The pouch may be constructed using several proven techniques such as the "J" pouch (Utsunomiya), "S" pouch (Parks) or side-to-side isoperistaltic pouch (Fonkalsrud). The pouch is advanced through the rectum, which is devoid of mucosa, and sutured to the anus. A temporary diverting ileostomy is done concomitantly to allow for healing of this anastomosis. Incorporating an ileal pouch and reservoir improves the functional results in a significant number of patients who undergo this type of operation with sphincter preservation.

Sphincter-saving operations for rectal cancer, chronic ulcerative colitis and familial polyposis improve the life-style for selected patients. Careful screening of patients in the preoperative period and careful postoperative evaluation and scrutiny are necessary to further determine the future role of these operative approaches.

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Splenic Salvage

SPLENIC SALVAGE is the preservation of all or part of the spleen as a planned surgical procedure, in contrast to total splenectomy. Until less than a decade ago, this approach was not only deemed heretical but was rarely practised anywhere in the world. Today it is widely accepted and done everywhere.

The impetus for splenic salvage was provided by the finding that the spleen plays an important role in the immunologic defense against sepsis, particularly infections caused by encapsulated organisms such as the pneumococcus and meningococcus.

The techniques of topical hemostasis for superficial splenic injuries and splenorrhaphy or partial splenectomy for more severe injuries have been well described in numerous reports. With these techniques, splenic preservation has been shown to be not only feasible but safe when used with judgment and care. Techniques using splenic fragments as omental implants are of debatable efficacy in maintaining immunologic competence and require further evaluation.

Although the major application of the concept of splenic salvage has been in splenic trauma, conservative splenic operations have also been described for splenic cysts and cases of Gaucher's disease.

The nonoperative management of splenic injuries has been a standard of practise in the selective management of splenic injuries in children, who are at high risk for overwhelming postsplenectomy sepsis. Recent reports describe the same mode of management used successfully in highly selected adult patients with known splenic injuries, if careful clinical observation indicates that bleeding from the injured spleen has ceased.

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Conservative Surgical Treatment of Carcinoma of the Breast

SURGICAL TREATMENT of primary carcinoma of the breast has changed significantly in the United States in the past decade. The radical mastectomy first gave way to the modified radical mastectomy as the surgical standard of care. Abroad, wide surgical ablation therapy has not been widely practiced. Proof by our foreign colleagues of the efficacy of conservative surgical treatment of primary breast carcinoma *coupled with* radiation therapy seems to be having an effect on surgical practice in this country.

Prospective randomized clinical trials abroad have shown the efficacy of breast conservation operation and radiation therapy in the local control of the disease with apparent long-term survival equivalent to that of regional excisional therapy. The foreign studies have shown local recurrence rates in the range of 5% at five years for non-mastectomy-treated patients. In retrospective studies, local recurrence rates during the sixth to tenth year following partial mastectomy and irradiation approach those of the first five years; thus, by ten years local recurrence rates are in the range of 12% to 14%. In the United States, early results of the National Surgical Adjuvant Breast Project have confirmed the findings of foreign studies. The final results of that study will be required, however, to show equivalent long-term survival in conservatively treated patients.

The effect of these studies on surgical practice in the US is beginning to be documented. A national survey has recorded the disappearance of the Halsted radical mastectomy, the increasing use of modified radical mastectomy and a threefold increase in the use of partial mastectomy between 1976 and 1981. Since 1981 the geometric increase in the use of partial mastectomy continues and appears to be resulting in a decreasing use of the total mastectomy therapy.

Attempts to standardize the surgical approach to breast conservation are beginning to be reported. Many questions concerning the technical details of conservative surgical treatment continue to be addressed. These include the exact handling of the primary tumor, the extent of resection of breast necessary and the extent of axillary dissection necessary to insure adequate staging of disease. The technical factors in-

volved in radiation therapy also are being addressed but are unsettled. However, nonmastectomy treatment coupled with radiation therapy for stages I and II carcinoma of the breast has established itself as a therapeutic option readily available to American women. Breast cancer continues to be a disease requiring multimodal therapy from the time of diagnosis.

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Editorials

Some Side Effects of Science and Technology on Medical Practice

NEW SCIENCE and new technology are in the process of transforming the world in which we live. In medical science and medical technology the pace of progress has been little short of phenomenal and, if anything, it seems to be accelerating. So far, medical practice has generally been able to keep up with this astonishing progress and apply it effectively in patient care. The result has been an enormous success—the best medical care the world has ever seen, and what the future holds simply boggles the imagination. This progress and this accomplishment have been fostered by government and welcomed by patients and the public. Even though the costs are soaring beyond any expectations (a better product usually costs more), there are still no signs that the public wants less health care.

But there is a downside to this record of scientific and technologic success that is a direct result of it. An unacceptable escalation of costs is already abundantly evident and a source of increasing concern, as is the quality of whatever care may be given at less cost. But there are other problems. Medical science itself is beginning to show some feet of clay. It is becoming common knowledge that many treatments in daily use are simply ineffective. Much of accepted medical practice is not all that scientific, and perhaps it is best that it not be. But there are concerns about the quality and costs of worthless treatments and about any harm that may be done by their use, and there is disillusion when science changes its mind, as it did in the recommended treatment of cancer of the breast, for example. And then there are scientifically indefensible variances in the way the same kinds of patients are treated for the same kinds of conditions with wide differences in the costs if not the quality of the treatments and services given. Yes, there is some clay on the feet of medical science and technology and some on the feet of physicians as well, since these are all problems of scientific medical practice. Unfortunately, physicians have been somewhat reluctant to examine problems such as these although they are quite clearly side effects of the successful application of new science and new technology in patient care. The result is that others than physicians and medical scientists are beginning to address these issues with whatever this may portend for physician leadership in medical practice and patient care.

In another dimension, there can be no question but that the accelerating progress in science and technology has had an increasing impact on what we like to call the art of medicine. This art, so important to patient satisfaction and to bringing the healing power of faith and trust to bear to relieve anxiety and suffering (and sometimes to effect a cure), is beginning to be replaced by a new art, that of sparring with patients about their care, dancing with the payors and, to the extent possible, avoiding becoming involved in claims of malpractice. The ancient art, which depends upon a trusting and understanding relationship between physician and patient, is being further weakened by the fractionation of patients into organ systems and of doctors into specialties and subspecialties, all to serve the imperatives of modern science and technology. In many instances patients are almost forced to deal with their own wholeness and in effect be their own doctors and make their own decisions about their health care. Or, missing the healing power and comfort of the art, they may seek solace, comfort and even curing from an ever increasing number of other often "nonscientific" health professionals who seem better able to provide them with what they need. One is reminded of Gresham's law in economics which predicts that bad money will always drive out good. In this case the good is what has always been a substantial part of a practicing physician's armamentarium. All of this can profoundly affect the practice of medicine and can have the effect of ceding much of its traditional role—and turf—to others.

Another side effect of science and technology in medical practice is the shifts that are occurring in decision-making in patient care. It still remains to be seen just how much hospital administrators, boards of trustees, managers of for-profit health care systems and others will be making medical practice decisions in the next few years, but they are likely to be increasingly interested and probably more involved because of cost factors. Another shift that is occurring in decision-making is exemplified by the recent "Baby Doe legislation" and the ethical and legal controversies about prolonging life at any age when there is little expectation that any reasonable quality of life will result. While admittedly none of these issues is fully resolved, the trend is for these kinds of medical practice decisions to be mandated by federal law, by courts or by others than the families and persons most concerned and their physicians. The power to decide these issues is being taken from the hands of those who must then live with the decisions that have been made for them.

We are again reminded that all of these problems of medical practice are simply the side effects of the successful application by physicians of new science and new technology in patient care. They are patients' problems and they are physicians' problems. Each one poses a challenge and an opportunity to provide leadership in finding a solution. They are inseparable from the new science and technology. They are inseparable from medical practice and patient care. Although the medical profession does not have the power it once had in health care, it is not impotent. It is well regarded in public opinion polls, and indeed much of the public is looking to physicians for help and guidance—yes, leadership—in dealing with these problems. As physicians and as a profession we now have an opportunity to provide the leadership to meet many of them head on by recognizing them for what they are and trying to do something about them. If this is done successfully it could mark yet another watershed in the marvelous evolution of our profession.

MSMW

Evaluation and Treatment of Impotence—Where Are We Going?

IMPOTENCE is a complex syndrome involving the interaction of psychological, hormonal, neurological, arterial, venous and sinusoidal factors. For socioethical reasons, the physiology of penile erection was not investigated and remained speculative and controversial for years. Consequently, most cases of impotence were regarded as a psychological disturbance and patients were ashamed to seek help.

In their article appearing in this issue, Davis and colleagues undertook the exhaustive task of investigating all the factors currently believed to cause impotence in aged patients and have demonstrated that the majority of their series of 93 are indeed suffering from a physical disease, not a psychological disorder. They have pointed out the inadequacy of traditional diagnostic studies, including nocturnal penile tumescence (NPT) monitoring, peripheral nerve conduction studies, psychological testing and Doppler penile brachial pressure index. They have also concluded that their extensive hormonal studies could not definitively establish a relationship between endocrine abnormality and impotence in the absence of a hormonal evaluation of age-matched potent men. They are to be congratulated for this undertaking. In this age of dollar consciousness, their costly study has disproved the merit of such an extensive investigation in every patient and has relieved us all of the guilt we might feel in using simpler approaches. (The total cost per patient for two nights' mercury strain-gauge NPT monitoring and evaluation of liver, renal and thyroid function, as well as measurements of fasting glucose, testosterone, estradiol, estrone, luteinizing hormone, follicle-stimulating hormone, prolactin and sex-hormone-binding globulin is about $1,200 in San Francisco.)

Fortunately, recent knowledge of penile vascular anatomy, neuroanatomy, pharmacology and hemodynamics has provided better insight into erectile function and dysfunction. Investigations of the detailed anatomy of the pelvic and cavernous nerves have elucidated the cause of impotence after pelvic, rectal, prostatic and urethral operations, and hundreds of patients have already benefitted from nerve-sparing techniques.[1,2]

Hemodynamic studies in human volunteers[3] and in animals[4,5] in which electrodes were implanted around the cavernous nerves have shown that erection involves the active increase of arterial flow, the active decrease of venous flow and sinusoidal relaxation. The relative contributions of the cavernous and pudendal nerves have been determined. Impulses from autonomic nerves (cavernous) will induce a *full erection*, with intracorporeal pressure around 80 to 100 mm of mercury; contraction of bulbocavernous and ischiocavernous muscles from somatic (pudendal) nerve impulses can further raise the intracorporeal pressure to 200 to 400 mm of mercury, resulting in the *rigidity* common to masturbation or sexual intercourse.

Most recently, the ability to induce penile erection by the intracorporeal injection of phenoxybenzamine and papaverine has further advanced the diagnosis and treatment of impotence.[6-8] Evaluation of the functional capability of penile arteries and veins is now possible. With duplex sonography and pulsed Doppler analysis before and after papaverine injection, the degree of arterial dilation and the amount of blood flow through individual cavernous arteries can be accurately measured.[9] In our preliminary studies with this technique, more than 75% of patients were found to have compromised arterial capability. Venous competence can also be assessed by erection cavernosography after either saline infusion or papaverine injection.

The advantage of papaverine injection is its ability to work locally, affecting the cavernous muscles and arterioles directly and bypassing neural influences. Our animal experiments[10] have shown that it fulfills all three requirements for penile erection: increased arterial flow, decreased venous flow and sinusoidal relaxation. It causes full erection when injected into the penises of normal volunteers as well as patients with psychogenic and neurogenic impotence. Those with neurogenic impotence can be differentiated by a characteristically hypersensitive and prolonged response. When used strictly for diagnostic purposes, papaverine injection is a safe procedure. Priapism has developed in none of our more than 200 patients studied thus far. However, several cases of priapism have been observed by others when papaverine was given therapeutically before sexual intercourse.

For the treatment of impotence, new methods of pharmacologic manipulation are being tried in several major centers in the United States, Canada and Europe: (1) intermittent papaverine injections, (2) self-injection of papaverine and phentolamine before intercourse, (3) self-injection of phenoxybenzamine before intercourse and (4) oral administration of yohimbine. It is hoped that these new advances will bring us a simpler and more physiologic approach to this puzzling problem.

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Food for Thought

KRONLUND AND PHILLIPS, elsewhere in this issue, report a survey of 128 physicians and surgeons to test their knowledge of the rates of death and major complications for ten common procedures and found that the overall accuracy of their knowledge of these rates was considerably lower than one might expect. Their results were a surprise and even somewhat of a

shock to this writer who likes to believe that published information on topics such as these becomes known to practicing physicians and influences their patient care decisions. The findings in this paper therefore raise some important questions, particularly in the present environment of medical practice, where physicians are expected to present state-of-the-art information to patients for shared decision making and informed consent for whatever procedure is to be undertaken.

Assuming the physicians in this study were considered to be competent (and there is no reason to suspect they were not), how does one account for such a wide lack of knowledge of existing published information? Perhaps our elaborate mechanisms for disseminating accurate medical information to physicians are not working as well as they should, or perhaps the information itself may not always have been thought to be accurate. After all, different case studies often give different rates for complications or deaths. Perhaps the data may not be considered to be current or specific to the situation where it is to be used, and therefore not relevant. It is certainly true that most physicians have been trained to be critical of experimental studies, particularly when the results do not seem to fit with their own professional experience. And all are aware that any individual patient may be anywhere along a curve of statistical probability. But none of these possible explanations seems fully to account for the wide lack of knowledge of existing information exposed in Kronlund and Phillips's study. There is much food for thought in all this, particularly as patient care evolves toward an ever more exact science, with practicing physicians expected to be authoritative for that science before their patients and the public.

MSMW

Stress and Coping in Internal Medicine Residency

ALTHOUGH THE HANDSOME and tireless intern in his scrub suit has been the subject of many romantic portrayals, there has recently been more serious attention in both the lay and medical press to the rigors of residency training and its effect on house officers. The article by Wolfe and Jones in this issue focuses on problems they have noted in the areas of professional socialization, conflicts between personal and professional life, "role strain," pregnancy and the role of the spouse. As the program they describe has a predominance of women, the authors feel they may be observing "gender differences in how residents are affected by and respond to certain problems in residency training." However, I question the validity and the productiveness of labeling difficulties experienced by women trainees as "women's problems." The exhaustion, uncertainty, fear and personal deprivation associated with residency affect both men and women. The culture of medicine remains predominantly male but that does not legitimize the labeling of the coping responses of women trainees as abnormal simply because they are different from the responses of men. The fundamental problem from which the maladaptive coping responses of men and women flow is the stress associated with residency training; thoughtful consideration of the origins of this stress is more likely to be fruitful for trainees of both sexes.

Training stress is a complex and incompletely described phenomenon. Some hardships of residency training are dramatic and readily identified; these include the extraordinary time demand and consequent physical and emotional exhaustion, the intense and sudden responsibility for life-or-death decisions and the tremendous amount of information to be mastered. Other aspects of residency training are perhaps equally stressful but less often appreciated. The daily work of a house officer, particularly an intern, is in large part unexpectedly monotonous. Teaching is unstructured and learning unpredictable. Ethical dilemmas in patient care are ubiquitous and typically are not explicitly addressed or resolved. The climate of a residency program is often inhospitable or overtly hostile to expressions of personal or professional distress. The list could be extended almost indefinitely by anyone who has recently completed an internship. Some of these hardships are inherent in the nature of medical work while others reflect oversight or traditions of training. In considering possible remedies, it is useful to view stress as originating in either the content, the process or the atmosphere of medical training. Once the source of stress has been firmly located, possible solutions tend to suggest themselves.

Challenges arising from the fundamental *content* of medicine relate to the overwhelming amount of medical knowledge, to the high level of uncertainty surrounding many major decisions, to the burden of responsibility for the well-being of other persons and to the ethical tensions frequently associated with this responsibility. Efforts to reduce training stress by direct manipulation of these fundamental attributes is unlikely to be effective or beneficial. However, explicit discussion of these issues in residents' reports, morbidity and mortality and attending rounds could promote a maturing understanding of the nature of medical practice in parallel with the development of technical expertise that already occurs during residency. Rather than suggesting that the best residents always know the right course of action, discussions should support the accurate identification of one's limitations and appropriate consultation. The pain, sadness, uncertainty and occasional error inherent in medicine should not be denied. Ethical tensions in the care of patients should be sought out and thoughtfully discussed. All of this would best be accomplished as an integral part of training by teachers who are also respected for technical competence. As these issues are part of medical practice, it is logical and natural that their discussions should be undertaken by practitioners in the course of caring for patients.

The challenges of the *process* of medical training include the extraordinary time demand and consequent exhaustion, the personal deprivation and family stress resulting from a workweek that is three times longer than that enjoyed by "normal people," the interpersonal demands of frequent rotation and team changes and the unpredictable nature of clinical teaching. These stresses reflect the traditions and habits of residency more than the fundamental nature of medical practice. Whether they should all be preserved is open to question. Recognizing the central importance of residents to the experience of everyone on a team suggests that more formal attention to the development of teaching and leadership skills could decrease interpersonal strain and increase team learning and the satisfaction that goes with it. Call schedules of every fourth night or better, alternating ward and consultation or clinic months and cross-coverage by a night float all offer the potential of humanizing the experience for residents without impairing learning or patient care.

The *atmosphere* of medical training may promote healthy or maladaptive responses to the challenges of medical training. Programs may give lip service to the idea that omniscience is not a training goal and that personal satisfaction should parallel professional development. But the selection of chief residents often appears to reflect a belief that successful residents subordinate personal life to profession, know all and never experience distress, uncertainty or conflict. A training program that by its actions supports unrealistic goals among house officers will increase training stress. A healthy residency environment accepts the accurate self-recognition of limits to knowledge and skill while motivating further learning, encourages the exploration of ethical issues involved in clinical medicine, actively promotes the acquisition of teaching and leadership skills in this residency, values personal development along with personal maturation and permits rather than penalizes expressions of training discomfort.

Having proposed this framework for considering residency stress, is there any reason to think that the challenges of medical training are more burdensome for women than for men? Before addressing this question directly, I wish to emphasize that difficulties experienced by women in training may reflect structural and institutional problems rather than "women's problems" per se. The fact that women may use particularly "feminine" coping techniques such as crying or particularly "masculine" techniques such as aggressiveness or cynicism does not necessarily indicate a more stressful experience but rather that their coping behaviors are more apparent in an environment where men have set the norms.

There is no reason to believe that women find the fundamental *content* of medical training more taxing than men. No one suggests that the ability to acquire a fund of medical knowledge, to shoulder life and death responsibility for patients and to deal with the ethical content and uncertain nature of many medical decisions is a sex-linked trait. The *process* of medical training is more problematic. Specifically, a 110-hour workweek can reasonably be expected to be burdensome to a woman with substantial commitments at home and a traditional family structure. Separation from small children for 36 hours at a time is wrenching. However, I am disinclined to consider the conflict between personal and professional commitments a problem for women alone and am more interested in the fact that men have for so long put up with "the myth of the heroic male professional." A well-developed personal life with inclination, time and energy for exercise, entertainment and companionship are presumably no less important for men than for women. Women do seem to experience increased conflict between personal and professional commitments in association with marriage and particularly with having children. I would again raise the notion that perhaps male physicians should have felt this conflict more strongly all along. Even pregnancy during residency, obviously a condition that is a predominant concern to women residents, has been accommodated in some training programs without difficulty. In our program seven women have had eight pregnancies without untoward disruption of the residents' schedules or individual training.

I suggest, finally, that it is in the category of *atmosphere* of medical training that women trainees may experience the most difficulty. Women are different from men and can be expected to cope differently and ultimately to practice somewhat differently. To the extent that men's behavior is considered normal, women will experience some unique training and practice discomforts. Rather than focusing on the reactions of one group of trainees, it seems to me far more productive to consider stress in training as the fundamental problem. In this way perhaps the residency experience can be reformed to the benefit of both men and women.

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Case Reports

Rhabdomyolysis and Acute Renal Failure Following the Bite of the Giant Desert Centipede *Scolopendra heros*

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ANIMAL VENOMS have been included among the reported causes of rhabdomyolysis.[1,2] There are several case reports of myoglobinuria and acute renal failure following snake bites and envenomation by bees, wasps and hornets.[3-9] We report a case of rhabdomyolysis associated with acute renal failure following the bite of the giant desert centipede, *Scolopendra heros.*

Report of a Case

The patient, a 44-year-old woman, experienced acute severe pain in her right foot while reaching under a bed in her home in an eastern Arizona mining town. On inspecting her foot, she found a 14- to 16-cm long centipede. In addition to pain, the patient noted swelling, numbness and discoloration of her foot, which progressed to involve her right leg over the next few days. She also suffered from fever, nausea, vomiting and shortness of breath and had blurry vision and near loss of consciousness. She was nonambulatory due to pain and swelling of her leg, but denied prolonged immobilization. She sought medical attention after three days and was treated with a regimen of erythromycin and prednisone. Her symptoms worsened despite therapy and she was referred to the University of Arizona Health Sciences Center five days after the centipede bite.

Her medical history included asthma and an allergy to bee stings, which was manifested as facial swelling and hives. Other than an occasional urinary tract infection, the patient had no known prior renal disease.

On physical examination at admission she was agitated but alert, noted to be obese and in moderate discomfort from pain. Her blood pressure was 162/104 mm of mercury, temperature 36.9°C (98.4°F), heart rate 100 per minute and respirations 30 per minute. She had expiratory wheezing on chest auscultation but no stridor. The entire right lower extremity was massively swollen, warm and tender, but not erythematous. A 3-mm superficial ulcerative lesion was present on the dorsal aspect of her right foot. There was decreased sensation to pinprick on the dorsal and plantar aspect of her right foot and total absence of motor function of her toes and ankle.

The admitting laboratory data showed pronounced azotemia complicated by a metabolic acidosis, hyperphosphatemia, hypocalcemia and hyperuricemia. The laboratory findings are summarized in Table 1. Analysis of urine showed a specific gravity of 1.010 and a trace of protein, with 2+ occult blood by dipstick. Microscopic examination of the urine identified two erythrocytes and one leukocyte per high power field. The renal anatomy was examined by ultrasound and the kidneys were of normal size and without evidence of obstruction.

Her admission chest radiograph was normal, and the arterial blood gas determinations done with the patient receiving supplemental oxygen by nasal cannulae showed adequate oxygenation.

Treatment with antihistamines, bronchodilators and steroids was initiated. Antibiotic coverage with erythromycin and cephalothin sodium was provided.

Hemodialysis was accomplished within 24 hours of admission. The urine output was never less than one liter per day. Nonetheless, she required hemodialysis on the second, third and fifth hospital days, after which she showed progressive renal recovery.

The right lower extremity remained painful and edematous. The anterior compartmental tissue pressures were 45 mm of mercury in the right leg and 25 mm of mercury in the left leg at the time of admission. An electromyogram on the third hospital day showed electrical silence of the peroneal compartmental musculature, denervative changes of the gastrocnemius and no stimulation of the peroneal or tibial nerves at sites above the ankle. Fasciotomies of the anterior and

TABLE 1.—*Summary of Laboratory Data on Selected Hospital Days*

Laboratory test	*Hospital Days* 1	2	10	26
Leukocyte count (per μl)	16,800	11,000	23,200	7,300
Hematocrit (%)	43.0	40.9	31.4	37.9
Serum sodium (mmol per liter)	124	124	138	140
Serum potassium (mmol per liter)	5.7	5.6	4.2	4.0
Serum chloride (mmol per liter)	87	89	102	103
Serum bicarbonate (mmol per liter)	15	12	26	27
Blood urea nitrogen (mg per dl)	160	162	53	15
Serum creatinine (mg per dl)	11.4	10.9	2.7	1.2
Serum uric acid (mg per dl)	...	15.8	7.3	...
Serum calcium (mg per dl)	7.4	7.6	8.7	...
Serum phosphorus (mg per dl)	11.2	10.2	4.2	...
Serum creatine kinase (IU per liter)	18,860	9,350	...	...
Serum albumin (grams per dl)	3.3	...	...	...
Arterial pH	7.36	...	...	...
Arterial P_{CO_2} (torr)	27	...	...	...
Arterial P_{O_2} (torr)	213	...	...	...

P_{CO_2}=partial carbon dioxide pressure, P_{O_2}=partial oxygen pressure

(Logan JL, Ogden DA: Rhabdomyolysis and acute renal failure following the bite of the giant desert centipede *Scolopendra heros.* West J Med 1985 Apr; 142:549-550)

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lateral compartments of the right leg with debridement of necrotic muscle were done on the fourth hospital day. Partial recovery of motor function was noted in the days following the surgical procedure, but four weeks after the bite of the centipede, recovery remains incomplete.

The patient was able by description and pictures to identify the centipede that bit her right foot as a giant desert centipede, *S heros*.

Discussion

Myonecrosis, anterior and lateral compartment syndromes and subsequent peroneal neuropraxis of the right leg developed as a consequence of envenomation by a giant desert centipede. Acute renal failure can be attributed to muscle injury and myoglobinuria in this circumstance as supported by the laboratory findings and subsequent course. To our knowledge, this represents the first documented case of rhabdomyolysis and acute renal failure due to the bite of *S heros*.

The giant desert centipede, *S heros,* is found in Arizona, southern California, Texas, Georgia, Alabama, Louisiana, Kansas and Mexico.[10,11] This centipede can attain a length of as much as 20 cm. The color of the head and posterior segment ranges from blue to chestnut brown.[11,12] There is little known about the precise components of the Scolopendromorph venoms, but hemolytic phospholipase A, serotonin and a cardiotoxic protein have been described in some species.[13,14] Furthermore, the toxin of the *Scolopendra* genus has been termed "cytolysin," referring to its ability to lyse cells.[12]

Articles on the effects of envenomation in humans generally imply that the venom causes a small focus of skin necrosis with only mild local pain lasting from hours to weeks. Systemic symptoms of vomiting, headaches and dizziness have also been described. There are rare reports of human fatalities, but the adequacy of the documentation of the cases has been questioned.[11] Generally, the scolopendrids have been described as relatively harmless to humans.[12,15]

This patient had significant morbidity as a consequence of *S heros* envenomation. The toxin induced not only local pain and swelling but myonecrosis with associated increases in the compartmental pressures in the leg, which led to compromise of neurologic function. Finally, acute renal failure due to rhabdomyolysis created a life-threatening condition that the patient fortunately survived.

Physicians practicing in the areas in which the giant desert centipede is found should be alert to the possible morbidity and mortality that can result from envenomation, which heretofore has not been widely appreciated.

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A Case of Hyperthyroidism Presenting as Recurrent Pneumonia

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HYPERTHYROIDISM generally presents as a well-recognized constellation of symptoms, including nervousness, fatigue, palpitation, weight loss despite good appetite, loose bowels, heat intolerance, tremor and excessive perspiration.

Sometimes, however, the involvement of one organ system can so dominate the clinical picture that initially the diagnosis of hyperthyroidism is missed. Such oligosymptomatic disease occurs especially in older patients who may have only cardiac symptoms. The usual hypermetabolic signs and symptoms may be totally absent. Patients appear apathetic and depressed. The initial evaluation of these patients yields few clues to the underlying condition. These patients often slip into a fatal thyroid storm that is equally apathetic and hard to detect. We report an unusual case of apathetic hyperthyroidism presenting as recurrent pneumonia.

Report of a Case

First Admission

The patient, a 57-year-old man, came to a community hospital because of chills, shortness of breath and chest pain. He had been in good health all his life except for nephrolithiasis and recurrent urinary tract infections requiring a series of operations seven years earlier.

Two months before admission, fever and sweats developed and the patient had cough and hiccoughs. Left pleuritic chest pain began one month later and the cough became productive of reddish brown sputum. The patient's family reported a six-month history of mental changes dominated by extreme forgetfulness and a decreased ability to concentrate. There was no history of weight loss, nervousness, change in bowel movements, tremor or heat intolerance.

He was seen at a community hospital where a chest x-ray

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film showed a right lower lobe infiltrate. Urinalysis showed gross pyuria. Treatment with ampicillin was given orally and the patient was transferred to the Albuquerque Veterans Administration Medical Center the next day. There he was admitted to the Medical Intensive Care Unit (MICU).

In the MICU the patient was noted to be lethargic and somewhat confused. His blood pressure was 128/80 mm of mercury, the pulse was 140 and irregular, respirations were 32 and the rectal temperature was 40.1°C (104.2°F). The patient was diaphoretic and hiccoughing. Examination of the head and neck showed no abnormalities. Rales and bronchial breath sounds were heard over the right lower lobe area. The cardiac impulse was felt at the anterior axillary line; no murmurs or gallops were heard. He had costovertebral tenderness on both sides. The rest of the physical examination showed no abnormalities.

A chest x-ray film now showed cardiomegaly, Kerley B lines, reversal of pulmonary blood flow to the upper lobes and a right lower lobe infiltrate with consolidation. A pyelogram done after dye was given intravenously showed a left renal calculus without evidence of obstruction. An electrocardiogram showed atrial fibrillation with a rapid ventricular response. The leukocyte count was 13,300 per μl with 78% polymorphonuclear cells, 20% lymphocytes and 2% monocytes. Urinalysis showed 30 leukocytes and 20 erythrocytes per high-power field with few bacteria. Culture of a urine specimen yielded no growth. Gram's stain of a sputum specimen showed many polymorphonuclear cells with Gram-positive cocci in pairs and chains. Sputum culture grew abundant *Staphylococcus aureus*. Blood gas determinations with the patient breathing room air showed a partial oxygen pressure of 58 and a partial carbon dioxide pressure of 25 mm of mercury and a pH of 7.49. Serum electrolyte values were normal. Congestive heart failure and a partially treated pneumonia were diagnosed. Administration of digoxin was begun and the antibiotic agents were switched to gentamicin sulfate and penicillin.

Over the first three hospital days the patient's pulse decreased to less than 100 but remained irregular. Fever persisted at a temperature of between 38.9°C (102°F) and 40°C (104°F) and methicillin sodium was added to the regimen to cover staphylococci. Although cultures of specimens of the patient's blood and cerebrospinal fluid obtained immediately following admission yielded no growth, he continued to be confused and at times combative. On the sixth hospital day his temperature dropped to 38.3°C (100.9°F). He was no longer combative, but still had pronounced short-term memory loss and was disoriented.

A low-grade fever along with the hiccoughs persisted until the tenth hospital day. The patient's rhythm reverted to normal sinus with the addition of quinidine sulfate to his drug regimen. The lung infiltrate continued to clear on x-ray study and the patient was discharged after two weeks in hospital.

Second Admission

The patient was readmitted two days later with nausea, vomiting, hiccoughing and left pleuritic chest pain. He was afebrile and the findings of a physical examination were unchanged. However, a chest x-ray film showed evidence of cavitation within the right lower lobe infiltrate and a new infiltrate had developed in the left mid-lung field.

At this time the patient was drowsy, disoriented and unable to sit up in bed. His deteriorating clinical condition and the radiologic progression of the pneumonia now suggested chronic aspiration, but no underlying cause for the patient's debilitated condition was found. A Tensilon test (edrophonium chloride) was negative for myasthenia. Carcinoma was suspected and bronchoscopy was scheduled.

On the fourth day of the second hospital admission, thyroxine (T_4) level taken routinely on readmission was reported to be 19 μg per dl. Administration of propranolol hydrochloride was started, 10 mg by mouth every six hours, causing dramatic overnight improvement. The patient was oriented, cooperative and able to sit up and eat. Over the next three days the propranolol dosage was increased to 40 mg every six hours and the patient became alert and ambulatory. In retrospect, it was recognized that the patient's voice had been weak and hoarse. His voice strengthened and a vigorous cough developed. On questioning at this time, the patient was able to report that he had had great difficulty swallowing, sometimes with food "going down the wrong way." During his first hospital stay, he had been unable to produce sputum without vigorous stimulation. This situation was now reversed with the propranolol therapy.

A barium swallow study done five days after initiating the propranolol therapy showed no abnormalities. An iodine I 125 scan showed a diffuse, toxic goiter. A regimen of propylthiouracil and oral penicillin was begun. The remainder of the patient's hospital course was uneventful, with gradual resolution of the lung abscess. The patient remained well during several months of outpatient follow-up.

Discussion

Lahey in 1931 first used the term "apathetic hyperthyroidism" to describe patients without the hyperkinetic behavior and hypermetabolic findings usually noted in cases of hyperthyroidism.[1] These patients were typically middle-aged or elderly women without eye signs and without noticeable enlargement of the thyroid. Death occurred in a stupor or coma without the usual agitation of a thyroid storm. Later studies have shown that oligosymptomatic or monosymptomatic thyrotoxicosis often presents with cardiovascular or neurologic manifestation predominating.

The patient described above was apathetically thyrotoxic. He had cardiac complications and a toxic delirium.What further delayed the diagnosis and complicated his course was the occurrence first of simple, then of recurrent, bilateral pneumonia, subsequently deduced to be caused by chronic aspiration.

The history and the physical findings obtained after the diagnosis of hyperthyroidism was made suggest that this patient had a bulbar palsy. Yet the patient's negative Tensilon test result argues against a diagnosis of concurrent myasthenia gravis. Myopathy in general, along with substantial weight loss, is common in cases of hyperthyroidism.[2] Yet our patient had no overt clinical signs of either. From 80% to 100% of patients will have some electromyographic evidence of a primarily proximal myopathy.[3] Bulbar myopathy, though, is a rare but well-described complication of hyperthyroidism. This usually occurs in association with chronic thyrotoxic myopathy and presents as decreased phonation and difficulty swallowing, which can progress to aspiration. However, an

"acute form" can also develop over a few weeks without limb paresis, as in this patient.

Kammer and Hamilton presented four cases of acute bulbar palsy with hyperthyroidism.[4] All of their patients' conditions were diagnosed as thyrotoxic and they then proceeded into early thyroid storm, at which time acute bulbar palsy developed. In one of their patients, the bulbar weakness also improved within 24 hours of the administration of propranolol therapy. Bulbar palsy has been reported with both acute and chronic, nonmyasthenic thyroid myopathy.[4-8] A case has been reported of a 56-year-old woman with three years of hyperadrenergic symptoms in whom thyrotoxicosis was diagnosed only after repeated bouts of pneumonia related to presumed bulbar palsy. Though myasthenia was not ruled out, her symptoms resolved with administration of carbimazole alone.[8]

It is interesting to consider why our patient's condition did not continue to deteriorate during his first admission. He was in storm with continuing aspiration. Yet this improved enough, although at a slow pace, that he could be discharged. It is possible that the intravenous pyelogram done the night of admission was more therapeutic than diagnostic. The contrast medium contained 18.5 grams of bound iodide. Because 1 to 2 grams of sodium iodide given intravenously is the recommended daily dose to suppress the toxic effects of goiter, it is possible that enough free iodide was released to suppress temporarily the release of thyroid hormone from the patient's gland and possibly to block peripheral conversion of T_4 to T_3. Fortunately, in this case, the large bolus of iodine without a preceding administration of propylthiouracil did not delay the response to specific antithyroidal therapy.

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ERCP Documentation of Pancreatic Ascites and Cystoenteric Fistula

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PANCREATIC ASCITES, transenteric rupture and bleeding are unusual complications of pancreatic pseudocysts.[1-3] Endoscopic retrograde cholangiopancreatography (ERCP) documented the occurrence of the former two events in a patient who subsequently suffered a fatal hemorrhage.

Report of a Case

The patient, a 29-year-old man with a history of chronic ethanol abuse, was admitted to hospital because of a two-week history of increasing abdominal girth, nausea, vomiting and abdominal pain. His medical history was significant for numerous bouts of pancreatitis, but no liver or ulcer disease.

On the admission physical examination, the patient was severely cachectic with profound temporal wasting and a grossly distended abdomen. In addition to the massive ascites, other physical findings were anicteric sclerae, rales at the left lung base and mild pedal edema. No abdominal masses or organomegaly could be appreciated and the stool guaiac was negative.

Laboratory data on admission included a hemoglobin of 15.1 grams per dl, a leukocyte count of 9,700 per μl and a serum amylase value of 360 units per liter (normal, 0 to 125) with ascitic fluid amylase of 4,900 units per liter and ascitic fluid albumin of 3.0 grams per dl. The ascitic fluid leukocyte count was 244 per μl (84% macrophages). An abdominal ultrasound study showed a cystic lesion in the head of the pancreas.

Central hyperalimentation via a Broviac catheter was begun and the patient's albumin level subsequently rose from a low of 1.8 to 3.1 grams per dl. It was thought that he could now tolerate an exploratory laparotomy and an ERCP was done. It showed a normal duodenum and papilla, normal biliary tree and gallbladder and a bilobed pseudocyst in the head of the pancreas with a fistulous tract from one of the pseudo-

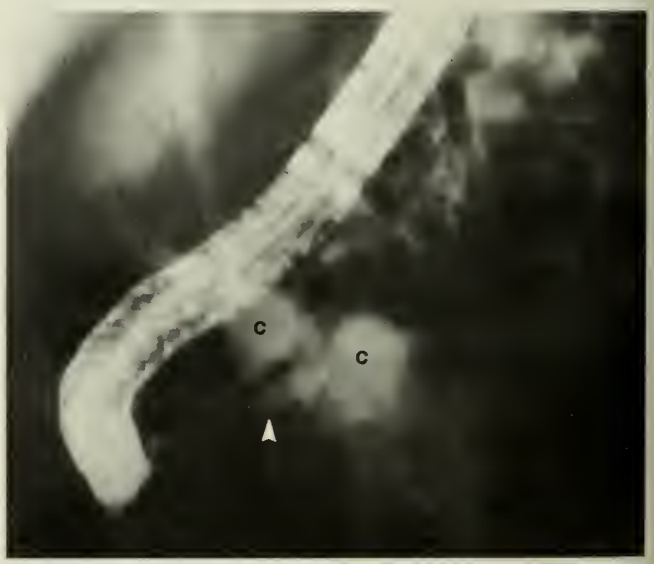

Figure 1.—Endoscopic retrograde cholangiopancreatogram showing two pseudocysts **(C)** in the pancreatic head, on either side of the main pancreatic duct **(arrow)**.

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cysts, which under fluoroscopic control was seen to end abruptly as the contrast medium streamed out into, and was immediately diluted by, liters of ascitic fluid (Figures 1 and 2). A repeat ERCP (done to unequivocally define the anatomy) was unsuccessful because of the inability of the patient to cooperate. During this aborted examination, however, although the duodenal bulb was noted to be normal, a 3-mm hole was seen in the duodenal wall in the postbulbar area proximal to the papilla. A contrast agent was injected into this hole via the ERCP cannula and a cystic structure with a communicating fistulous tract was opacified (Figure 3). A gastrointestinal series done a day after the ERCP was interpreted as showing either a large ulcer in the superior fornix of the duodenal bulb or, alternatively, barium pooling in the remnants of a pancreatic pseudocyst that had eroded into the duodenum (Figure 4).

Unfortunately, as the patient was being prepared for a surgical procedure, he signed out of hospital only to return 12 hours later with coffee-ground emesis and a profound drop in hemoglobin. A nasogastric tube was placed that showed bright red blood but despite vigorous resuscitative measures the patient exsanguinated.

A limited autopsy carried out by the county coroner showed that there were no esophageal varices; the stomach contained blood clots and there was a large crater in the duodenum extending into the head of the pancreas. The pancreas itself showed fibrous changes and areas of calcification but no obvious pseudocysts.

Discussion

Most cases of pancreatic ascites are due to alcoholic pancreatitis; together with those cases generated by traumatic pancreatic injuries, they account for greater than 95% of reported occurrences.[1,4]

Before the definitive studies of Cameron and co-workers[5]

Figure 3.—Fistulogram showing the connection between the duodenal wall and the partially collapsed pseudocyst (**C**).

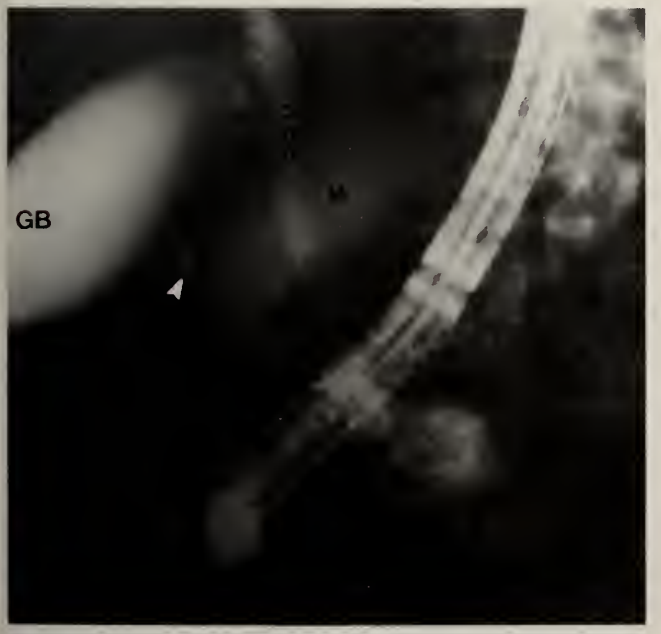

Figure 2.—Another film from the initial endoscopic retrograde pancreatocholangiogram showing the fistulous tract and actual site of leak (**arrow**). Leaking contrast is momentarily pooling in the hepatorenal space (Morison's pouch, **M**). **GB** = gallbladder, **cbd** = common bile duct

Figure 4.—Spot films from the gastrointestinal series showing persistent collection of barium in the region of the duodenal bulb. Contiguous air (**arrow**) suggests that these findings represent cystoenteric rupture into the duodenal bulb.

that suggested that pancreatic ascites was caused by a pancreatic duct disruption, other theories erroneously proposed that blocked intraperitoneal lymphatics or subacute peritoneal inflammation, or both, were causes of pancreatic ascites. The irritation of the peritoneum by pancreatic secretions results in the high albumin levels noted in pancreatic ascitic fluid; albumin is *not* secreted by the pancreas. However, with the increasing use of retrograde pancreatography in evaluating patients with pancreaticobiliary disease, it has been shown unequivocally that pancreatic ascites is caused by a tear in a major pancreatic duct or from disruption of an incompletely formed pseudocyst.[2,6] In the case presented above, a fistulous tract from one of two pancreatic pseudocysts located in the head was clearly found to be emptying into the peritoneal cavity.

In addition to the complication of pancreatic ascites, our patient also had transenteric rupture of a pseudocyst into the postbulbar duodenum. This was recorded by the endoscopic visualization of a hole in the duodenal wall that, when cannulated and injected with a contrast agent, was shown to be a pseudocyst with a connecting fistulous tract. Transenteric cyst rupture can occur in any part of the adjacent gastrointestinal tract, with one series showing an equal predilection for the stomach, duodenum and colon. Rarely, pseudocysts have been noted to rupture into the esophagus or small bowel.[3]

Although transenteric rupture of pancreatic pseudocysts may result in resolution of the cysts, this occurrence is not without its hazards. Half of these events are associated with gastrointestinal hemorrhage and, in one series, all seven deaths complicating cystoenteric rupture were attributed to massive bleeding.[3,7] Presumably this hemorrhage is the result of through-and-through erosion of the bowel wall caused by the adjacent pseudocyst or erosion into nearby vessels during the process, or both.

Such may actually have been the cause of death in our patient. Although no ulcer was seen endoscopically at the time of either ERCP, a barium study showed a "probable" ulcer in the duodenal bulb. Closer inspection of these films, however, showed air in what could very well have been the remnants of the second pseudocyst, which had ruptured into the duodenal bulb (the first one rupturing into the postbulbar duodenum). Supporting this hypothesis is the fact that the limited autopsy, albeit a superficial one, failed to show any residual pancreatic pseudocysts and that the crater in the bulbar area was adherent to the pancreatic head. Furthermore, a recent case report described the findings of a barium study that suggested a duodenal ulcer, which subsequent endoscopy and fistulography confirmed to be a tract from the duodenal bulb into a pancreatic pseudocyst.[8]

The vascular anatomy in the region of the pancreatic head and duodenal bulb is such that it would not be at all difficult to implicate an acute erosion into a branch of the gastroduodenal artery to account for the rapid exsanguination in our patient.

A reasonable approach to the treatment of pancreatic ascites would be to attempt medical therapy for several weeks. Central parenteral hyperalimentation will "rest the pancreas" and perhaps allow a fistula to close spontaneously; some physicians successfully treated pancreatic ascites with irradiation.[9] In these cases it is theorized that low-dose irradiation (550 rads) did not induce fibrosis but rather an acute, reversible diminution in enzyme secretion that contributed to healing of the ductular tear or decreased the leakage from a pseudocyst.

Most patients with pancreatic ascites will not respond to medical therapy but will at least have had improvement of their nutritional status before the major surgical procedure required. The success of surgical intervention is clearly related to accurately locating the leak, as Sankaran and colleagues reported a recurrence rate of 53% in 19 patients who had no pancreatogram, but no recurrences in 7 patients with endoscopic localization.[10] ERCP constitutes state-of-the-art preoperative diagnostic management in these patients, and although it uncommonly shows the leak as clearly as in the case presented here, it will define the ductular anatomy, its relationship to pseudocysts, if any, and afford surgeons a road map before they embark on a perilous surgical journey.

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Maggot Therapy Revisited

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THE BENEFICIAL EFFECT of maggot therapy on wound debridement has been known to surgeons since ancient times.[1] Baer popularized this method when he reported in 1931 the successful treatment of 89 cases of intractable osteomyelitis by the application of blowfly larvae.[2] Maggot therapy flourished during the next ten years, but its popularity soon waned with the introduction of antibiotics and antiseptic solutions. Today, the intentional use of maggots for the treatment of chronic wounds has been nearly abandoned.

In this report we describe a case of a patient with a ne-

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crotic facial tumor that was infested with maggot larvae when the patient first presented for treatment. The larvae were left in situ and successfully debrided the wound before surgical therapy.

Report of a Case

The patient, an 88-year-old woman, was referred from a local convalescent hospital to the Emergency Room of San Francisco General Hospital Medical Center with a chief complaint of maggot invasion of a facial tumor. The patient did not recall the duration of the lesion and, due to poor vision, was unaware of the presence of the larvae. She said she did not have facial pain, pruritus or fever. On examination she had a 4×4-cm raised, necrotic ulcer over the right upper cheek. The wound contained several blowfly larvae; there was no evidence of surrounding cellulitis or palpable adenopathy. Her overall hygiene was otherwise normal and physical examination showed no abnormalities. A tentative diagnosis of squamous cell carcinoma was made and confirmed by an incisional biopsy.

In light of the innocuous appearance of the wound and an agreeable patient, we elected to continue supervised wound care using resident maggots (Figure 1). The exact species of the blowfly larva was not determined. The wound was covered with a sterile moist saline dressing and observed several times a day. By the third day the wound was found to be clean and void of any necrotic residua. The remaining maggots were then removed by topically applying ether.

One week after admission, the facial lesion remained free of necrotic tissue and larvae. Cultures of surface wound showed a scant growth of contaminating bacteria. The lesion was excised and closed with a local transposition flap. Postoperative recovery was unremarkable and the patient returned to her nursing home.

Discussion

Baer's 1931 report describing the use of blowfly larvae for the treatment of chronic osteomyelitis heralded a decade of investigation into the physiologic basis of maggot therapy.[2] One must recall that during this period the mortality for compound lower extremity fracture was 75%, mainly due to the complications of osteomyelitis. In his series of 89 patients with chronic osteomyelitis, Baer reported a success rate of 90% using maggot therapy—especially remarkable considering that some of his cases involved tuberculous osteomyelitis and other intractable lesions. During the 1930s and early 1940s, maggot therapy was used successfully for a variety of other suppurative infections including abscesses, burns, gangrene and chronic leg ulcers. Stewart defined the ideal lesion to treat with maggot therapy: a shallow wound with a relatively large amount of necrotic tissue.[3] Robinson found that the number of maggots per wound varied from 200 to 600, which consumed an average of 10 to 15 grams of necrotic tissue a day.[4,5]

The life cycle of the maggot, larva of one of several blowfly species of the Calliphoridae family, has been studied by Baer and others.[2,3,6,7] Baer found that maggots could be secured by exposing raw beef outdoors on which flies would deposit their eggs. Blowflies will also deposit eggs in open wounds or parts of dead birds and animals not covered by feathers or hair, and occasionally on feces. The eggs hatch in 8 to 24 hours and the larvae begin feeding. The newly hatched maggots secrete a proteolytic enzyme capable of extracorporeal digestion, following which the liquefied food is swallowed into the alimentary tract and perhaps absorbed through the integument. Within a week or two, the larvae convert into pupae, and this is followed by the emergence of flies a few days later.

Early attempts at maggot therapy were occasionally followed by the unfortunate appearance of anaerobic infections. Of these, *Clostridium perfringens* and *Clostridium tetani* infections were most worrisome. Attempts to sterilize maggots by soaking them in hydrogen peroxide were unsuccessful. Although the bacteria could be initially eliminated from the surfaces of the larvae, endogenous intestinal tract bacteria survived and soon recolonized externally. Baer discovered, however, that the surfaces of unhatched fly eggs could be successfully sterilized by soaking them in a bichloride solution at room temperature for one hour. This technique produced sterile larvae that could then be reared in a sterile environment until they were applied to a wound. The potential for causing a nosocomial infection was thus eliminated.

The success of maggot therapy is not limited to their scavenger action. Robinson suggested that maggot products—allantoin, urea and, most important, ammonium bicarbonate—have considerable healing properties.[8] Other proposed benefits of maggot therapy, most of which remain unproved, have included rinsing out and dilution of bacteria in a wound as a result of the serous exudate induced by the presence of maggots, enhancement of granulation tissue formation by the continuous crawling of the larvae, enzymatic liquefaction of necrotic tissue, destruction of wound bacteria in the alimentary tracts of the maggots, the use of necrotic tissue for food by larvae, the secretion of antibacterial agents by the larvae, increased wound alkalinity and the release of various other agents supposedly beneficial to wound healing (such as calcium picurate, sulfhydryl, amino acids and the like).[5,6,9-11] Vistnes and co-workers have suggested that a suitable form of

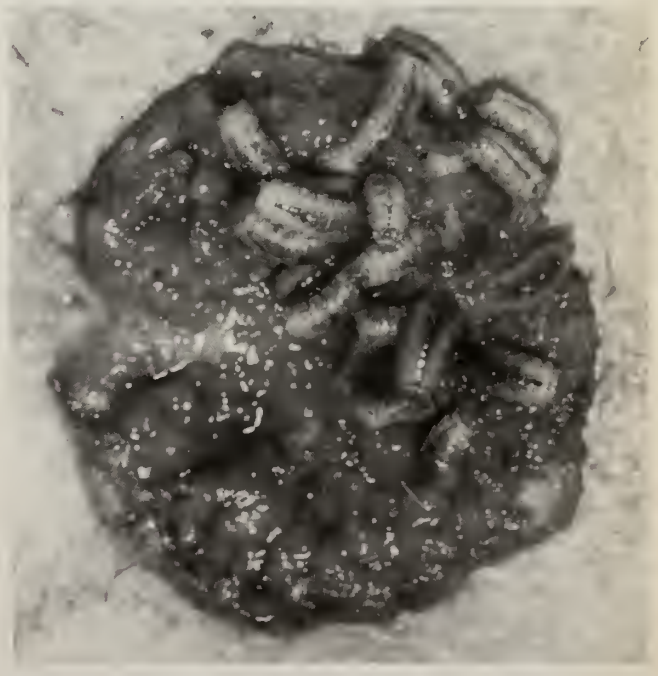

Figure 1.—Full-grown larvae present in a cheek wound of an 88-year-old woman on the second hospital day.

maggot proteolytic secretions could be useful for enzymatic wound debridement.[12]

Maggot therapy has certain undeniable advantages: blowfly larvae consume only necrotic tissue, thereby leaving vital structures unscathed; maggots act topically and are not reliant on an excellent peripheral blood supply; maggots are universally available, and maggot therapy is outstandingly cost-effective.

The chief disadvantage of maggot therapy is an aesthetic one. In this post-Listerian era, it is difficult to convince hospital staff and patients of the potential benefits of maggot therapy. Another possible disadvantage of maggot use is the incitement of an intense local pruritus (noted by earlier investigators). Our patient, however, was oblivious to the maggots' presence—a factor that allowed us to continue their use until the wound was debrided.

The dawning of the antibiotic era effectively brought a halt to the popularity of maggot use for wound debridement. Due to social disapproval, it is unlikely that maggot therapy will ever regain the level of popularity it enjoyed in the 1930s and 1940s. As recently as 1976, however, Horn and associates showed that maggots may be used successfully to treat a case of subacute mastoiditis unresponsive to conventional therapy.[13]

Despite a rather extensive armamentarium in wound therapy, contemporary physicians occasionally encounter a special sore in a special patient in a special circumstance that dictates special care. While not advocating a step backward in time, we feel that this unique, albeit unconventional, approach to wound management may occasionally deserve consideration.

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AACIA CASE HISTORY CONTEST

The American Association of Clinical Immunologists and Allergists will be starting a new section in its journal, *Immunology and Allergy Practice*, entitled "The Case History of the Month."

In order to generate interest in this new feature, Searle Pharmaceutical Company will be sponsoring a contest consisting of a $300 prize for the best paper in each of the following categories:

1. A physician in private practice,
2. A physician in academics,
3. A physician in training.

These case reports may be in any field relating to allergy, clinical immunology, obstructive pulmonary disorders or related ear, nose and throat problems.

An original and two copies of each paper should be sent, along with the category in which the physician would like to be considered. The contest deadline is December 31, 1985. Correspondence should be addressed to:

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Correspondence

The Editorial Board will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words, and must be typewritten, double-spaced and submitted in duplicate (the original typescript and one copy). Authors will be given an opportunity to review any substantial editing or abridgement before publication.

Treatment and Prevention of Fat Embolism Syndrome

To the Editor: In reviewing the article "Fat Embolism Syndrome,"[1] I was disappointed to read the limited discussion on therapy and prevention.

In 1974 Horne and Horne, of Salt Lake City, reported on a successful program for the prophylaxis of the fat embolism syndrome.[2] Basically, treatment of a susceptible person with intravenously administered hypertonic glucose (with or without insulin) prevents the mobilization of fat molecules. In the ten-year interval since publication, the authors confirm that no cases of fat embolism syndrome have occurred in their practices using this prophylactic regimen despite their managing many patients with multiple large bone fractures. It would seem many others could benefit from such a successful regimen.

Unfortunately, no mention was made of this article which comes from our own western area. I hope this will bring it to the attention of those who read the *WJM* article.

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Methodology in Study of Youthful Suicides

To the Editor: I am writing regarding the article "Death in the West—A Regional Analysis of the Youthful Suicide Rate,"[1] which appeared in the June 1984 issue. Although the results are fascinating, I have several questions about the methodology:

1. On pages 969 and 970 it states, "Once the suicide incidence figures were collected for every state for each of the 15 years I calculated suicide rates using data from the 1970 US Bureau of the Census[2] as the population denominator." Does the author mean that he used 1970 census counts by age (15 to 24 years) for each state for each five-year period—that is, 1964-1968; 1969-1973; 1974-1978?

Unless one makes the assumption, which does not appear in the article, of linear increases in population for each state during this 15-year period, for the western states the author has artificially lowered the rates in 1964-1968 and artificially raised them for 1974-1978.

2. The analysis is not symmetrical (or balanced) in terms of the years selected. Why did the author not group 1968-1972, giving two years around the census, rather than one year before and three years after?

3. The 1964-1968 group contains data from two to six years before the census, while the 1974-1978 group contains data from four to eight years after the census. The year groups are not equal around the census and are biased in reference to the denominator, the 1970 census.

I realize that Dr Seiden wanted to use the latest data available, 1978, but why did he not group the data differently—for example, 1963-1967; 1968-1972; 1973-1977?

4. On page 969 the author states, "Data were gathered on the incidence of suicide among 15- to 24-year-olds in each of the 50 states and the District of Columbia." However, he does not say whether these are residence or occurrence data. Although I assume he used residence data, the statement is not clear.

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* * *

Dr Seiden Replies

To the Editor: With respect to the methodological questions raised by Marvin Levy, let me answer them as best I can. Questions 1 through 3 are basically variations on the question of my use of the 1970 census figures for a population denominator. I used these data as the best available population figures. The intercensal years are (sometimes rather inaccurate) estimates so I felt that I was better off using the census count itself. It is correct that I was assuming a linear increase (or decrease or balance) in state populations, but this is a reasonable assumption although it should have been made explicit. Mr Levy has answered questions 2 and 3 himself: I wanted to use the latest available data (1978), therefore the slightly asymmetrical groupings. While his critical points may affect

the absolute validity of the data to a slight degree, I do not think it has much bearing on the more important comparative rankings by state. If a difference of a year or two would affect the results to any pronounced degree, that would require significantly unstable and erratic population behavior. Empirical observation of population estimates does not reveal such a pattern. Indeed, a linear assumption seems far more warranted as I see it.

Finally, the question of incidence data: Mr Levy's assumption is correct, I used residence data. Actually, the assumption of residence is rather fluid (at least here in California) and it is pretty difficult *not* to be classed as a resident if you have made any efforts towards establishing residence or, in some cases, even expressed an interest.

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Reporting Requirements for Reye's Syndrome and AIDS in California

To the Editor: Your California readers may be interested in recent changes in the reporting requirements for Reye's syndrome and acquired immunodeficiency syndrome (AIDS).

Effective January 1, 1985, Section 304.5 of the California Health and Safety Code mandates the reporting of Reye's syndrome to public health authorities within seven days of diagnosis. Until now, the California Department of Health Services (DHS) has depended on voluntary reporting by physicians and hospitals to obtain data about the occurrence, severity and distribution of Reye's syndrome in California.

Over the last 15 years, between 15 and 25 cases of Reye's syndrome have been reported each year. About a third of these cases have been fatal. However, the actual incidence is believed to be substantially greater than voluntary reporting indicates. It is hoped that the new law will improve epidemiologic information about the syndrome and, consequently, provide better clues about its etiology—especially with regard to the presumed association with aspirin. It is also hoped that better reporting of Reye's syndrome will allow health departments to monitor the effectiveness of the warning label that the aspirin industry has recently agreed to place on aspirin containers.

AIDS was made a reportable disease (Section 2503, California Administrative Code, Title 17, California Health and Safety Code) in March 1983. Initial reporting of this disease seemed to be relatively complete; however, in the past year there has arisen increasing evidence that more and more physicians do not report AIDS because they fear that the information will not remain confidential. This is not true. The DHS regards reports on patients, whatever the disease, as medical records and treats them with the strictest confidentiality. This confidentiality is guaranteed by law. Information from case reports is used only for statistical purposes and to protect the public health.

It is important that AIDS case reporting be as complete as possible so that trends in the spread of the disease, both geographically and temporally, as well as among various segments of the population, can be monitored. These data also serve to identify new risk factors should they emerge.

The prescribed forms for making these reports (the Confidential Morbidity Report) can be obtained from local health departments or the Infectious Disease Section of the California Department of Health Services.

Both Reye's syndrome and AIDS are important public health problems. A great deal more must be learned about both conditions, and we urge all physicians to comply with the reporting requirements for these diseases.

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Neonatal Seborrheic Dermatitis

To the Editor: The distinction between seborrheic dermatitis and atopic dermatitis could be very difficult, if not impossible, to make in very young infants. Moss suggests that seborrheic dermatitis appears earlier in life—the first few weeks rather than two to three months—than atopic dermatitis.[1] I would like to report my experience with a neonate who presented with seborrheic dermatitis in the first few days of life. To my knowledge, this is the youngest infant with seborrhea reported in the literature.

Report of a Case

A male infant weighing 3,810 grams was born at term to a gravida 3, para 2, 33-year-old mother following an uncomplicated pregnancy and normal vaginal delivery. There was no history of birth trauma. Apgar scores were 8 and 9 at one minute and five minutes, respectively. At eight hours of age, an erythematous rash appeared on the face and the postauricular areas. Twenty-four hours later, the rash became scaly with mild involvement of the scalp. The neonate looked quite comfortable and the lesions did not seem to be pruritic. There was no family history of atopy. The infant was seen in consultation by a pediatric dermatologist who agreed with the diagnosis of seborrheic dermatitis. After treatment with 0.5% hydrocortisone cream there was pronounced improvement and subsidence of the rash in two to three days.

The diagnosis of seborrheic dermatitis in this case was based on its early appearance in life, its involvement of the scalp and postauricular area, its nonpruritic nature and its rapid response to treatment with steroid cream. An eosinophil count is not of much aid in the differentiation of seborrheic and atopic dermatitis.[2] When the diagnosis is in doubt, total and specific IgE levels will aid in their differentiation; these levels are elevated in patients with atopic but not seborrheic dermatitis.[2] The distinction between these two conditions is important as the latter has a more favorable prognosis and a lesser chance of recurrence.

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Abolish Medi-Cal

To the Editor: As a general practitioner in a less affluent area, I believe physicians have a responsibility to treat those unable to pay, and therefore am enrolled as a Medi-Cal (Medicaid) provider. I do not expect much profit from this arrangement, but recent experiences have left me chagrined at the built-in unworkability of the Medi-Cal system and contemplating my financial losses.

A few examples will help make my point. A sick young woman came to my office and I diagnosed thyrotoxicosis after a thorough workup. I also irrigated her ears on the same occasion, at her request. Claims were submitted to Medi-Cal for a complete physical and for ear irrigation. Medi-Cal paid me a few dollars for the ear irrigation and denied payment for the physical, due to a rule that if a "procedure" is paid for, no other service can be paid for on the same visit. When I wrote back and offered to withdraw the claim for the ear irrigation if they would pay for the physical, they refused. This is a case of getting less for doing more.

On another occasion, trying to plan ahead, I called the Medi-Cal office and inquired whether they would pay for annual physicals. I was informed they would pay and was given the applicable RVS code. When I submitted claims for physicals with the code given, the claims were rejected with the explanation that Medi-Cal does not pay for this service. I believe this is also known as Catch-22.

Another problem involved the drainage of an abscess, for which I billed with the appropriate RVS code. The claim was rejected due to absence of a "modifier" code, with instructions to consult the Medi-Cal manual or call a certain number for information. My office attempted to call the number for an entire day. When, miraculously, someone answered, by the time I got to the phone (about 30 seconds later), they had hung up. The manual is six inches thick and I have no clue where to find the needed data.

I have come to the conclusion that Medi-Cal is not a system for paying for medical care to the poor; it is a system for denying payment for such medical care. I realize that if I continue to treat poor patients, it will be at my own expense.

My recommendation is that this absurd Medi-Cal program be abolished, and the patients rely on charity or county facilities. It is especially infuriating to contemplate the tax dollars spent on salaries for the administrators of this outrageous fraud. The money would be better spent on health-promoting endeavors such as accident prevention and programs to curtail alcohol, tobacco and drug abuse.

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Eicosapentaenoic Acid, Heart Disease and Iron

To the Editor: Eskimos have a very low incidence of acute myocardial infarction. Dyerberg and Bang[1] have suggested that they may be protected from acute myocardial infarction by their high plasma levels of eicosapentaenoic acid and other omega-3 polyunsaturated fatty acids. These substances are thought to protect Eskimos from the thromboembolic complications of cardiovascular diseases by reducing platelet aggregability.

I wish to suggest an alternative hypothesis on the relationship between high eicosapentaenoic acid intake and the observed low incidence of ischemic heart disease in Eskimos. Reduced platelet aggregability should not only prevent thrombosis in the coronary arteries but should also induce a bleeding tendency. Increased bleeding times have in fact been found in Eskimos and in volunteers on a diet high in eicosapentaenoic acid.[2] A chronic tendency to bleed may cause a decrease in iron stores because of increased loss of blood (and iron), especially from the gut. The observed low incidence of ischemic heart disease in Eskimos may be primarily a result of iron depletion caused by high plasma levels of eicosapentaenoic acid, reduced platelet aggregability and chronic blood loss from the gut and other sites.

This suggestion is a corollary to the hypothesis that iron depletion protects menstruating women from heart disease.[3,4] Iron depletion or deficiency appears to be a common feature of several conditions associated with reduced incidence of ischemic heart disease: poverty in developing nations, vegetarianism, the long-term use of aspirin or cholestyramine[5] and premenopausal status. In the case of menstrual iron loss, reversal of the condition by simple hysterectomy or natural menopause is associated with both iron repletion and an increased incidence of heart disease. A reduction in the amount of menstrual iron loss such as that observed with the use of oral contraceptives may be associated with an increased risk.

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Percent of Fat in Meat, Poultry and Seafood

To the Editor: The article "Diet and Health" by Gotto and co-workers in the December issue[1] contains several apparent factual errors as well as some distortions or misrepresentations worthy of comment.

First the factual errors: The authors state, "Seafood, including shellfish and finfish, provides less fat per gram of protein than poultry, beef or pork." Though some seafood is indeed quite low in fat, many types, such as anchovies, herring, mackerel, sardines, shad, trout, tuna (in oil) and eel, are very high in fat (greater than 50% of calories). Other fish that are moderately high in fat (30% to 50% of calories from fat) include albacore, carp, salmon and tuna (drained of oil).[2]

Second, cocoa butter is referred to as a source of saturated fat and is then grouped with other saturated fats that are sources of elevated levels of serum cholesterol. In 1970 Grand and co-workers[3] reviewed the literature on the relationship of cocoa butter and chocolate with cholesterol levels and added further experimental evidence showing that stearic acid (the primary saturated fat in cocoa butter) lacks cholesterol-

raising properties. This apparently little known relationship has been overlooked by a number of writers who continue to list cocoa butter (or chocolate) as a saturated fat that raises serum cholesterol levels.

Third, the authors state that removing chicken skin before cooking decreases the fat that penetrates the lean tissue, but add, "This is not true for turkey; therefore, the skin does not need to be removed before cooking." Since cooked turkey skin is 84% fat,[2] by calories, it seems unlikely that this fat would not also penetrate the lean tissue as it does in chicken.

The distortions or misrepresentations (which I have no reason to suspect are intentional) concern the discussion and listing (in Table 2) of the percent of fat in meat, poultry and seafood. Instead of considering fat content of these foods as percent of total calories, the fat content is listed as percent by weight. The latter gives the impression of a distinctly lower quantity of fat (than is actually there)—see Table 1. Reading the percent of fat by weight tends to give readers a false sense of security when consuming any of the items listed.

Though I would emphasize that I agree with the authors' general advice, I do take issue with the statement, "If lipids reach an acceptable level with only a moderate restriction of fat and cholesterol, that is the level at which a person should be maintained, not a more restricted one." First, "acceptable level" is vague and therefore not very helpful. Though the acceptable level is clearly debatable, I think that most now agree that it is well below the 90th percentile figures which the authors describe as "the upper limits of normal." Second, it has become apparent that reducing fat in the diet is likely to reduce several kinds of cancer risk (as well as several other pathologic conditions).[4,5] Therefore, advising maintenance of only moderate fat restriction as long as cholesterol levels are acceptable denies the patient the other potential benefits that a more restricted fat intake can provide.

Finally, as noted by the most recent American Heart Association joint statement of the Nutrition Committee and the Council on Arteriosclerosis (of which Dr Gotto was a member), "There is the possibility that people whose cholesterol levels are at the upper end of the putative desirable range may still be at higher risk for coronary heart disease than those at the lower end; if so, a maximal reduction of levels may be beneficial."[6] They added, "The recommended diet may reduce risk in ways that are not reflected in plasma lipid values; saturated fats and dietary cholesterol possibly have adverse effects on lipoprotein metabolism not revealed in fasting lipid levels."

TABLE 1.—*Percent of Fat in Meat, Poultry and Seafood (by Weight, as Represented by Gotto, and by Calories, as Calculated by Freedman)*

	Percent Fat (by weight)	*Percent Fat (by calories)*
Seafood		
Clams, raw	2.5	21
Flounder, raw	0.8	9
Haddock, raw	0.1	10
Salmon, pink (humpback), raw	3.7	28
Snapper, red and gray, raw	0.9	9
Shrimp, raw	0.8	8
Tuna, water packed	0.8	6
Tuna, oil packed	8.2	37
Poultry		
Chicken, light meat, no skin, roasted	4.5	18
Chicken, dark meat, no skin, roasted	9.7	32
Chicken, light and dark meat with skin, roasted	13.6	53
Turkey, light meat, no skin, roasted	3.2	20
Turkey, dark meat, no skin, roasted	7.2	37
Turkey, light and dark meat, with skin, roasted	9.7	39
Beef		
Flank, round (lean only), cooked	6.1	29
Chuck, porterhouse, T-bone (lean only), cooked	10.3	42
Ground beef, regular, cooked	20.3	64
Lamb		
Shoulder (lean only), cooked	9.6	47
Pork		
Ham (lean only), cooked	9.0	39
Spareribs (lean and fat), cooked	35.1	77
Luncheon Meat and Sausage		
Bologna, beef	28.4	74
Italian sausage, cooked, pork	25.7	76
Pepperoni, pork and beef	43.9	83
Salami, dry, pork	33.7	76
Summer sausage, beef and pork	29.9	76

*Percent fat by calories calculated by multiplying grams of fat/100 grams edible portion times 9 (approximate calories/gram) divided by total calories/100 grams edible portion, then multiplying result times 100.

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Dr Gotto and Ms Scott Reply

TO THE EDITOR: In his letter to the editor, Dr Gerald C. Freedman describes "factual errors," "distortions" and "misrepresentations" in our article, "Diet and Health." He has raised several highly technical points and in every instance we believe that he is wrong. We do agree with him concerning the vagueness of the phrase "acceptable lipid level," however.

Dr Freedman raises the issue of how to interpret data on the fat content of food. It can be presented as either percent by weight or percent of calories. In relative terms, comparable results are achieved—that is, in a list showing fat content in descending order, by either method, the same foods appear first, second, third and so forth. Fat content by weight is the accepted format. The US Department of Agriculture often uses this method for classifying foods. It is used by meat and dairy companies for identifying fat content (1% fat milk, 96% fat-free meat). Most diet materials are written to teach the consumer to use percent fat (by weight) with nutrition labeling. Of course, the numbers are lower with percent per weight than with percent of calories. Both systems require education for use.

Seafood is classified by the US Department of Agriculture

according to percent fat by weight (100 grams), not percent calories from fat.[1] The low-fat fish category ranges from less than 1% fat to 5% fat. Medium-fat fish is 6% to 15% and over 15% is high-fat fish. According to this classification, cod, haddock, flounder, ocean perch and most species of tuna are "low-fat." Mackerel, albacore tuna and most species of salmon are in the medium-fat group. Eel, seer mackerel and chinook salmon are high-fat fish. Herring ranges from 4.4 to 16.4 grams fat per 100 grams. Shellfish falls in the low-fat category, having total lipid ranging from less than 1% to 3.6% fat.

The article states that seafood provides less fat per gram of protein than poultry, beef or pork. This is true for shellfish and low-fat fish, which make up most of the seafood consumed. The ratio of fat to protein is 0.005 to 0.16 for low-fat, 0.33 to 0.65 for moderate-fat and 0.82 to 1.15 for high-fat fish.[1] Chicken ranges from 0.15 to 0.5, beef 0.19 to 2.07 and pork 0.39 to 1.03. Recent studies have shown that fish oil is rich in ω-3 fatty acids and lowers plasma triglycerides and cholesterol in some instances. Harris and co-workers[2,3] showed that when normal subjects ate salmon filets and salmon oil, total cholesterol and triglyceride decreased 11% to 17% and 34% to 40%, respectively, over four weeks. Salmon and mackerel, high-fat fish, are good sources of ω-3 fatty acids. Although "technically" high-fat fish does not have less fat per gram of protein than poultry, beef and pork, it is still the "preferred choice" on lipid-lowering diets.

Cocoa butter is a saturated fat by structure. It contains 59.6 grams of saturated fat in 100 grams total fat, with 33.2 grams provided by stearic, 31.6 grams from oleic and 25.4 grams from palmitic.[4] Grande and associates compared the effects of cocoa butter and palm kernel oil with "imitation cocoa butter" and "imitation palm kernel oil." The mean serum cholesterol levels were 203±29, 199±29, 217±34 and 193±31 mg per dl for cocoa butter, imitation cocoa butter, palm kernel oil and imitation palm kernel oil, respectively. The imitation cocoa butter consisted of palm oil, hydrogenated soya-bean oil (mostly stearic), olive oil and safflower oil yielding the same fatty acid composition as cocoa butter. Since the cocoa butter and the imitation cocoa butter gave similar results, the effects on serum cholesterol were due to the fatty acid composition and not to some peculiar property of cocoa butter. McGandy and Hegsted[5] concluded from their review of several studies that "the data support the thesis that stearic acid has less effect upon serum cholesterol than lauric, myristic, or palmitic acids, but do not support the contention that it is completely without effect under most conditions."

In reference to Dr Freedman's comment about removing skin on chicken before cooking and not removing turkey skin before cooking, we used Agriculture Handbook No. 8-5 on poultry products.[6] When chicken is cooked with skin, by dry heat, retention is 192% total lipid, whereas for turkey it is 128% total lipid. According to Posati (L. P. Posati, US Department of Agriculture, oral communication), there is so little transfer of fat from the skin on turkey that it is not advisable to remove it before cooking because of the "drying" of the meat that could occur. Feely and associates[7] say, "there would seem to be no advantage in cooking turkey meat without skin, as the cholesterol does not appear to transfer from skin to meat during cooking." Skin on turkey should, however, be removed before it is eaten. Chicken skin is 32.4% fat, and turkey skin is 36.9% fat.[6]

We agree with Dr Freedman that "acceptable lipid level" is vague. But, it is well below the 90th percentile. Since the time our paper was written, the National Institutes of Health held a consensus conference on lowering serum cholesterol levels. The committee agreed that "review of all available data suggests that levels above 200 to 230 mg/dl represent values above which most would agree that there is an increased risk of developing premature coronary heart disease." They further define "high risk" and "moderate risk" as shown in Table 1.

TABLE 1.—*High Risk and Moderate Risk Serum Cholesterol Levels, as Defined by National Institutes of Health Committee*

Age Years	Moderate Risk mg/dl	High Risk mg/dl
2-19	>170	>185
20-29	>200	>220
30-39	>220	>240
40+	>240	>260

Moderate risk values are approximately between the 75th and 90th percentiles and high-risk the 90th percentile, as determined by the Lipid Research Clinics Prevalence Study.[8]

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Topics in
Primary Care Medicine

Physical and Occupational Therapy for Arthritis

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"Topics in Primary Care Medicine" presents articles on common diagnostic or therapeutic problems encountered in primary care practice. Physicians interested in contributing to the series are encouraged to contact the series' editors.

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Physical therapy modalities, because of their essential role in relieving symptoms and improving function, have long been accepted for treating arthritis patients. Modalities such as heat, cold, exercise, joint protection and splints help to relieve pain and maintain or increase joint range of motion, muscle strength and level of function within the limitations posed by arthritis. The use of certain physical measures also decreases unnecessary stress and thereby reduces the risk of needless joint damage or aggravation of disease symptoms. These results help improve the quality of life for patients who must live with a chronic illness.

Physical therapy and occupational therapy provide or instruct patients in the use of these modalities (Table 1). Overlap occurs between the disciplines, particularly in exercise and training areas, so physicians should contact local therapists if they have questions about appropriate referrals.

Because of the chronicity of various forms of arthritis and the need for regular therapy, the major emphasis of a treatment program is self-management. Therapists teach patients techniques appropriate to their individual problems, with the aim that they can then do these regularly at home. Such a program needs periodic evaluation and supervision by a therapist and a physician to motivate compliance, adapt the program to a patient's changing condition and assure realistic patient expectations that these therapies relieve symptoms but do not cure disease or repair joints. Patients require a series of therapy visits (two to three times a week) only if they have difficulty learning a self-care program, need assistance from a therapist to do the activities or need special equipment available only in a therapy department. Educating patients in a self-management program is always essential.

Pain Relief Measures

Heat and cold are most frequently used for pain relief. They increase the pain threshold and aid in muscle relaxation, thereby improving joint range of motion. Heat also increases tendon extensibility. Effects on actual joint temperature may vary with the joint treated, modality used and type of arthritis.

Patients frequently report greater pain relief with cold, especially for acute, severe pain or a hot joint, but heat is often more soothing for chronic, dull pain when the joint is cool. Both heat and cold have been shown to decrease stiffness, but most patients prefer heat for relieving morning stiffness. Dry heat can be tolerated at a higher temperature whereas moist heat penetrates more, and most patients prefer moist heat. Both cold and heat are contraindicated where there is scar tissue, hyposensitivity or hypersensitivity or circulatory insufficiency; cold is specifically contraindicated in cases of Raynaud's phenomenon, cryoglobulinemia and paroxysmal cold hemoglobinuria. The efficacy of one type of heat or cold treatment compared with another has not been established, so patient preference and ease of home use guides the choice of modality.

Patients should be taught several modalities for home use. Baths and showers are preferred for heating many joints, but equipment such as tub rails and bath benches may be needed as well as instruction in appropriate, safe techniques. Individual joints may be heated or cooled with moist heat packs, heating pads, cold packs or ice. Hands and feet can be submerged in warm water where exercise can also be done. Specific instruction for all modalities is necessary to insure safety.

Melted paraffin and oil provide heat to hands or feet in physical therapy departments and can, with the use of a crock pot or home paraffin unit, be used at home. Paraffin can be tolerated at a higher temperature than water (52°C to 54°C [126°F to 130°F]) and provides lubrication of the skin, which is particularly helpful in cases of scleroderma. Because it is complicated to do at home and dangerous if not done correctly, it should be used only when other modalities are unsuccessful and after careful training.

Modalities providing deep heat (ultrasound and dia-

(Simpson CF: Physical and occupational therapy for arthritis [Topics in Primary Care Medicine]. West J Med 1985 Apr;142:562-564)

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TABLE 1.—*The Uses of Physical Therapy Compared With Occupational Therapy*

Indications for Referral	*Therapist Will Teach/Provide*	
	Physical Therapy	*Occupational Therapy*
Musculoskeletal pain or spasm	Heat, cold, massage, traction	Splints, joint-protection techniques, adaptive aids
Decreased joint range of motion	Exercises	Splints
Decreased muscle strength	Exercises	Adaptive aids
Fatigue	...	Energy conservation, work simplification
Postural difficulty	Exercise, postural training	
ADL difficulty, such as personal care, work, homemaking, leisure	...	ADL training, adaptive aids, joint protection
Gait or mobility difficulties	Ambulation aids, gait training, shoes, inserts, wheelchair training	Wheelchair training
Joint operation	Preoperative and postoperative exercise	Hand exercises, splints
Nerve compression	Traction	Splints (carpal tunnel)

ADL=activities of daily living

thermy) require trained personnel and special equipment and are therefore impractical for regular home use. Deep heat is contraindicated for an acutely inflamed joint and has not been shown to be more effective than superficial heat for symptom relief in cases of chronic arthritis. Ultrasound is beneficial with periarticular problems, such as capsulitis or bursitis, and for increasing tissue extensibility for improving range of motion.

Although caution is needed with tender joints, massage can relieve pain, particularly that related to muscle spasm, and the techniques can be taught to a family for home use. Cervical and lumbar traction may also relieve pain by reducing muscle spasm and resultant nerve root pressure in patients with osteoarthritis of the spine. It is contraindicated for patients with inflammatory arthritis (especially rheumatoid arthritis) who have ligamentous or boney destruction and subluxation of the cervical spine. Many of the joint protection techniques and devices also decrease pain by protecting joints from unnecessary stress.

Exercise

Exercise plays a vital role in improving and maintaining physical function in a patient with arthritis. A therapeutic exercise program (based on evaluation of individual problems) maintains or improves specific joint motion or muscle strength, and a general exercise program such as swimming or bicycling augments this program while increasing general physical fitness and endurance.

The amount and kind of exercise is important to consider. Exercise can be harmful if inappropriate or excessive and may increase intraarticular pressure, inflammation and possible joint damage. Both therapeutic and general exercise must be adapted to patient problems including the type of arthritis, the stage of disease and joint involvement if a patient is to participate appropriately. Acute disease activity (inflamed joints or increased fatigue) necessitates fewer repetitions of exercises, and damaged joints cannot tolerate heavy resistance in exercises or activities. Increased pain is to be avoided. If these guidelines are followed, people with arthritis who remain active show better disease outcomes than those who do not.

Patients maintain or increase joint motion through range-of-motion exercises. Active exercise is preferred to passive, as a patient can accommodate movements to pain while also contracting muscles that may be seldom used. Assistance in stretching soft tissues should be done with therapeutic supervision and never on an acutely inflamed joint. Certain positions, such as gravity-free positions, also facilitate movement with less pain.

Isometric exercises (contraction of a muscle with minimal joint motion) strengthen muscle with little joint stress or increase in inflammation and are therefore the exercises of choice for patients with inflammatory arthritis or severe joint damage. Isotonic exercises (resistive exercises with joint motion) put a patient at risk for increased pain, inflammation or joint damage and should be used cautiously with therapeutic supervision and only when a disease is not active and joints are not severely damaged. Isokinetic exercises (constant resistance at a controlled rate of movement) seem less stressful than isotonic with careful use but require specialized equipment in a therapy department and are therefore not practical for long-term programs for patients with arthritis.

Besides strengthening muscles, arthritis patients need to increase endurance, particularly after long periods of relative inactivity. A general conditioning program is recommended for patients in the chronic stages of systemic disease or for nonsystemic joint problems, and should include high-repetition, low-resistance activities (swimming, bicycling or walking) that avoid stress on severely damaged joints (no jogging on damaged knees). Such programs augment therapeutic programs when chosen with a patient's particular disease or problems in mind—that is, swimming for a patient with ankylosing spondylitis enhances shoulder range of motion, erect posture and chest expansion.

Thermal and physical properties of water can also be used to facilitate exercise in a therapy pool or any accessible heated pool. Buoyancy can assist range of motion by supporting limbs and aiding movement and can decrease weight bearing for mobility activities such as walking. Viscosity adds graded resistance to exercise if speed of movement is regulated. Concurrent heat decreases pain and further facilitates movement. Patients with severe active disease or joint damage often exercise with ease in warm water when land exercise is not possible.

To derive maximal benefit with minimal risk from an exercise program, patients must understand their disease process, recognize changes in their overall condition and specific joints and differentiate pain from joint discomfort. They can then alter their exercise program daily—that is, by decreasing the number of repetitions or not moving joints as far—as disease activity changes.

Adaptive Measures

Adaptive measures include the various devices and techniques of joint protection and energy conservation. Training in the use of these measures enables people with arthritis to participate as independently as possible in all areas of life while minimizing pain and stress to their joints.

By adapting the way in which activities of daily living are carried out, patients can participate in activities previously too difficult or painful while protecting their joints from unnecessary stress. For example, a person with shoulder pain and decreased motion may move frequently used objects to lower shelves or learn special techniques for putting on clothes. Special devices such as long-handled sponges and brushes may enable them to wash their backs or brush their hair. Environmental adaptations may be made to position shelves, clothes rods and so forth to within easy reach. A thorough analysis of a patient's physical limitations, the environment and the task to be done allows a therapist to tailor methods and adaptations to specific needs.

Orthoses such as splints, braces and collars are helpful aids for arthritis patients. Probably the most frequently used orthoses for cases of arthritis are splints. Static splints immobilize a joint for rest and proper positioning or support a joint to increase function and thereby decrease pain and joint stress. Dynamic splints allow controlled motion in specific planes, mobilize joints and provide skeletal and muscle balance (often postsurgical splints). Custom-made splints (as opposed to prefabricated ones) appear more comfortable to arthritis patients and better fit individual deformities and joint changes.

Braces and collars are less frequently used than splints. The amount of bracing needed to support a weight-bearing joint may be too heavy for an arthritis patient weakened by systemic disease or by inactivity. Soft collars provide enough support to allow some muscle relaxation and pain relief for osteoarthritis patients but provide no protection for a rheumatoid patient who has cervical subluxation, in which case a Somi or halo brace is needed. Patients wearing splints, braces or collars must also do exercises daily to maintain joint range and muscle strength or the orthoses will contribute to the problem being treated.

Gait training with appropriate ambulation aids enables a patient to maintain mobility by decreasing weight bearing on involved joints and thereby decreasing stress and pain. Aids include canes, crutches and walkers, with canes being appropriate for those who need minimal to moderate assistance for one extremity and crutches and walkers for those who need more assistance for one or both lower extremities. Patients with hand involvement may require special hand grips or platform (forearm weight-bearing) crutches or walkers. Patients with shoulder or elbow involvement or elbow nodules may find even these adaptations useless, and very weak patients may find them too heavy. Essential training in the use of a device promotes safe and effective use of the aid.

Appropriate shoes include a low, wide heel, large toe box, cushion soles and soft but supportive leather uppers. Patients with metatarsophalangeal (MTP) joint involvement or pronation will probably also need a custom-made shoe insert to shift weight bearing behind the MTP heads (instead of an external MTP bar) and to counteract the other deformities. An orthotist, physical therapist or occupational therapist may construct these inserts. An expensive option is a custom-made shoe, designed to accommodate all foot problems, which offers a wider variety of styles for a fashion-conscious patient.

Summary

The therapy program described herein most closely approximates that for a relatively mobile person living at home, which is the status of most arthritis patients. However, the program for a patient in hospital or an acutely ill or homebound patient would vary only in its specifics, such as the amount and difficulty of exercises and activities and the assistance needed. Acutely ill or in-hospital patients may do fewer, easier activities, with an emphasis on maintenance of joint and muscle function and education in future activities. A homebound patient may need more assistance (equipment, personnel) and environmental adaptations but have fewer exercise and activity precautions. Only in a mentally compromised patient or one permanently confined to an institution will self-management with increased independence not be the major goal.

The benefits of such a program should be made available to all patients with chronic arthritis. Through the regular use of a self-management program, patients can prevent unnecessary pain and loss of function and thereby live more productive, satisfying lives. Obviously, not all arthritis patients will need all parts of the program, but they must be given an opportunity to learn how to use the physical modalities they need; otherwise their arthritis care is incomplete.

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Physician Knowledge of Risks of Surgical and Invasive Diagnostic Procedures

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Knowledge of the rates of major complications of surgical and invasive diagnostic procedures is essential to effective clinical decision making. A mail survey of 128 family or general physicians and general surgeons in Washington state tested their knowledge of the rates of death and major complications for ten procedures. Overall accuracy of physician knowledge was low, with 27% of responses correct, 26% underestimates, 27% overestimates and 21% admitting no knowledge. No significant differences in accuracy were found between specialty groups. Few associations were found between accuracy and physician board certification, years in practice or performance of the procedure. For every complication, many physicians made underestimation or overestimation errors by several orders of magnitude and a few consistently denied existence of any risk. Physicians could improve their knowledge of the rates of complications associated with procedures they carry out.

(Kronlund SF, Phillips WR: Physician knowledge of risks of surgical and invasive diagnostic procedures [Health Care Delivery]. West J Med 1985 Apr; 142:565-569)

No surgical or invasive diagnostic procedure is without risk of complication. Accurate knowledge of these risks and their rates of occurrence is essential to sound clinical judgment. Three major reasons may be cited. First, complications can be better prevented or managed if they are anticipated. Second, knowledge of risk is integral to risk-benefit analysis. Without accurate knowledge of a procedure's complication rates, one cannot validly balance the scales of risk and benefit in making a surgical decision. Third, when seeking informed consent before any procedure is undertaken, the patient deserves, and the law expects, full and accurate disclosure of the attendant risks. It is not sufficient to describe only those risks that "come to mind" or to state that a certain risk occurs "only rarely" or that "I have never seen it happen."

This knowledge is essential not only to the physician doing a given procedure, but also to the primary care physician who must initially assess the clinical situation and determine whether a surgical referral is indicated. Furthermore, following a surgical consultation, a patient may return to his or her primary care physician seeking assistance with the decision to proceed with an operation or to pursue other therapeutic options.

Surgical decision making has been the object of increased study in recent years. Rutkow and Zuidema have discussed the factors involved in surgical decision making with the goal of judging whether or not a given procedure might be "unnecessary."[1] Eiseman and Wotkyns have attempted to add objectivity to this area by developing clinical decision trees for a number of invasive procedures.[2] Others have explored the role of second opinion programs as a guide to appropriate surgical utilization.[3] Still others have suggested that cost-benefit analysis is useful in this area.[4,5] Yet no published study has measured physician knowledge of the risks accompanying surgical or invasive diagnostic procedures. This study examines physician knowledge of the risks of selected surgical and invasive diagnostic procedures, compares the knowledge of family or general physicians with that of general surgeons and identifies relationships between accuracy of this knowledge and other physician characteristics.

Methods

Ten common surgical and invasive diagnostic procedures were selected and the surgical literature was reviewed to establish the reported rates of death and one well-recognized complication for each procedure. Procedures were selected for which there was consistency in the published literature regarding rates of death and complications. The complement of procedures covers a wide range of death and complication rates. Some of the procedures chosen are commonly carried

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ABBREVIATIONS USED IN TEXT

FP/GP = family or general physicians
GS = general surgeons

out by family or general physicians, general surgeons, or both, while others are done only rarely by physicians in these specialties, though these physicians may care for and refer patients requiring these procedures. The ten procedures and the published rates for death and complications are outlined in Table 1.

The study group was drawn from the membership of the Washington State Medical Association on the basis of their self-identified specialty: a 157-physician sample of the 1,439 family or general practitioners (FP/GPs) and a 169-physician sample of the 412 general surgeons (GSs). Within each of these specialty groups names were selected randomly using a random number table. Both sample sizes were set to be approximately equal to 160. These physicians were mailed a brief, anonymous questionnaire asking them to estimate the death rate and a specified complication rate for each of the ten procedures by choosing an order of magnitude ranging from 1/10 to 1/100,000. Respondents were directed to "indicate to the best of your knowledge the approximate risk of occurrence for each" of the listed complications. For some of the questions certain patient groups were specified to allow closer matching of the physician's response with the published rates (for example, death from inguinal herniorrhaphy in patients aged over 60 years). Responses were considered correct if they matched the order-of-magnitude category most closely corresponding to that reported in the literature. Respondents were asked to estimate the death or complication rate attributable only to the procedure and attendant anesthesia and not to the underlying disease process. In addition, the respondents were asked to record the yearly number of their patients requiring each procedure and the number of such procedures they personally carried out. Physicians were also asked to describe their medical educational background and their current practice setting.

The overall questionnaire return rate was 46.3% (151). The return rate for FP/GPs and GSs alike was 42% (66 and 71, respectively). Eleven were excluded because the physicians reported their specialty as something other than FP/GP or GS. Twelve excluded themselves from the study for reasons including retirement, illness or living out of state. The remaining 62 FP/GPs and 66 GSs make up the total study group of 128.

Physician groups were compared for differences in their estimates using χ^2 analysis. Multiple-regression analysis was used to examine the association between the accuracy of physician estimates and specialty, board certification, number of years in practice and personal performance of procedures. An alpha level of 0.05 was used as the criterion for statistical significance.

Results

The GSs were significantly more likely to be board certified: 88% of the GSs were board certified as compared with 60% of the FP/GPs. The two groups were remarkably similar, however, in terms of practice experience and current practice settings. FP/GPs averaged 19.9 years in practice while GSs averaged 18.4 years. The practice structure and

TABLE 1.—*Reported Rates of Death and Complications for Ten Surgical and Diagnostic Procedures*

Procedure	*Reported Mortality Rate (%)*	*Rate Used for Study**	*Complication*	*Reported Complication Rate (%)*	*Rate Used for Study**	*References*
Interval cholecystectomy for cholelithiasis . .	0.28 (women aged 50-69)	1-9 / 1,000	Subhepatic abscess	0.27	1-9 / 1,000	6, 7
Elective inguinal herniorrhaphy	1.8 (patients >60 years old)	1-9 / 100	Recurrence following initial Cooper's ligament repair for indirect hernia	3.3	1-9 / 100	8-10
Suction curettage abortion < 12 weeks gestational age	0.0012	1-9 / 100,000	Hemorrhage (>250 ml)	0.07-0.15	1-9 / 1,000	11-14
Transurethral prostatectomy	1.3-2.5	1-9 / 100	Permanent incontinence	0.5	1-9 / 1,000	15-17
Vaginal hysterectomy	0.13	1-9 / 1,000	Ureteral injury	0.2	1-9 / 1,000	18
Pneumonectomy	11.9	1-10 / 10	Empyema	<5.0	1-9 / 100	19-21
Cerebral angiography	0.06-0.1	1-9 / 10,000	Femoral thrombosis	0.05-0.4	1-9 / 1,000	22-24
Interval tonsillectomy following peritonsillar abscess	0.006	1-9 / 100,000	Hemorrhage	1.0-2.0	1-9 / 100	25, 26
Coronary angiography via percutaneous femoral artery catheterization	0.11-0.78	1-9 / 1,000	Myocardial infarction	0.1-0.22	1-9 / 1,000	27-30
Subtotal thyroidectomy	0.07	1-9 / 10,000	Permanent superior laryngeal nerve paralysis	0.9	1-9 / 100	31, 32

*The Rate Used for Study identifies the order of magnitude representing the bulk of reported data.

location of the two physician groups were also similar, though FP/GPs were more commonly practicing in the smallest communities.

A variety of surgical procedures were carried out by FP/GPs, as shown in Table 2. For most procedures, however, the GS group reported more physicians doing the procedure and a higher number of procedures done by each physician. The exceptions to this trend were that more FP/GPs did tonsillectomies and suction dilation and evacuation procedures. As one might expect, neither group had extensive involvement with either of the radiographic procedures, and neither group carried out transurethral prostatectomies.

Table 3 summarizes the estimates of death and complication rates made by the entire study group for all ten procedures. No significant differences were found in the accuracy of risk estimates between FP/GPs and GSs: 27% of the responses given by FP/GPs were correct versus 26% for GSs. No systematic differences were seen between the specialty groups in direction of errors as underestimates or overestimates. For purposes of discussion, therefore, the estimates given by these two physician groups are considered together.

Multiple-regression analysis showed few significant associations between accuracy of physician estimates of risk and physician characteristics. When estimating death from vaginal hysterectomy, general surgeons more often tended to be correct or to overestimate than FP/GPs. Those physicians of either specialty who were not board certified tended to underestimate this risk. Noncertified physicians also tended to un-

TABLE 2.—*Procedures Carried Out by Family/General Physicians and General Surgeons in the Study Group*

	Family/General Physicians (N=62)			General Surgeons (N=66)		
*Procedure**	*Physicians Using Procedures (%)*	*Procedures Done per Year Mean† (SD)*		*Physicians Using Procedures (%)*	*Procedures Done per Year Mean† (SD)*	
Cholecystectomy	17.7	5.3	(3.3)	92.4	35.8	(19.9)
Herniorrhaphy	30.6	7.8	(3.2)	95.5	42.9	(26.1)
Suction curettage abortion	9.7	13.0	(13.2)	1.5	25.0	(. . .)
Transurethral prostatectomy	0	. . .	(. . .)	0	. . .	(. . .)
Vaginal hysterectomy	4.8	3.7	(1.2)	21.2	13.2	(9.0)
Pneumonectomy	0	. . .	(. . .)	40.9	5.8	(3.1)
Cerebral angiography	0	. . .	(. . .)	3.0	7.5	(3.5)
Tonsillectomy	25.8	7.8	(7.0)	12.1	13.5	(10.4)
Coronary angiography	0	. . .	(. . .)	0	. . .	(. . .)
Thyroidectomy	1.6	2.0	(. . .)	84.8	7.9	(6.0)

All figures based upon physician self-report.

*See Table 1 for further description of the specific procedures.
†Mean number of the specific procedures per year among those physicians carrying out one or more such procedures.

TABLE 3.—*Estimates of Death and Complication Rates for Ten Procedures by Family/General Physicians and General Surgeons*

*Procedure**	*Specific Complication Rate**	*Never Occurs (%)*	*Physicians Underestimating† (%)*	*Physicians Answering Correctly‡ (%)*	*Physicians Overestimating (%)*	*Did Not Know (%)*
Cholecystectomy	Death	6	32	41	15	6
	Subhepatic abscess	6	24	29	32	9
Herniorrhaphy	Death	6	77	6	2	9
	Recurrence	5	20	52	14	9
Suction curettage abortion	Death§	2	. . .	13	50	35
	Hemorrhage	1	6	16	41	36
Transurethral prostatectomy	Death	2	51	17	4	26
	Incontinence	2	6	20	46	26
Vaginal hysterectomy	Death	4	34	32	12	18
	Ureteral injury	3	19	26	32	20
Pneumonectomy	Death‖	3	57	20	. . .	20
	Empyema	3	19	43	13	21
Cerebral angiography	Death	2	2	19	48	29
	Femoral thrombosis	2	6	20	41	31
Tonsillectomy	Death§	2	. . .	17	56	24
	Hemorrhage	1	15	46	14	24
Coronary angiography	Death	2	17	35	20	28
	Myocardial infarction	1	5	22	44	28
Thyroidectomy	Death	5	17	28	43	8
	Nerve paralysis	6	47	35	5	8
Total¶		3	23	27	27	21

*See Table 1 for further description of procedure and specific complication.
†Excludes "never occurs" responses, which can be added to give total percent physicians underestimating reported rate.
‡See Table 1 for reported rates.
§Survey instrument will not allow this rate to be underestimated.
‖Survey instrument will not allow this rate to be overestimated.
¶Figures rounded to nearest whole percent.

derestimate the risk of ureteral injury during hysterectomy. When estimating the risk of death from thyroidectomy or the occurrence of subhepatic abscess following cholecystectomy, those physicians with more than 20 years of practice experience tended to underestimate. Finally, physicians who do tonsillectomies were more likely to correctly estimate the associated death rate than those who do not do the procedure.

Comments

Physicians in our study group possessed limited knowledge of the death and complication rates for the ten selected procedures. Only 27% of the total risk estimates fell within the order of magnitude reported in the literature. Across all ten procedures, underestimation and overestimation errors occur equally as often (26% and 27%, respectively). In the remaining 21% of responses, the physician admitted no knowledge of the particular rate. This distribution suggests little more than a random choice among four possible categories. Even more surprising is that for each procedure at least one physician explicitly stated that the complication in question "never occurred" or had a rate of "zero" or "none."

No particular pattern of underestimation or overestimation was identified. Estimates of death in elderly patients undergoing herniorrhaphy were the least accurate and most underestimated of any of the survey items (see Figure 1.) Substantial percentages of physicians underestimated the risk of death due to herniorrhaphy by a factor of 100 or even 1,000. Included in this group that made gross underestimates were many physicians who did the procedure regularly. Estimates of recurrence following herniorrhaphy, however, yielded the highest number of correct responses. To illustrate the other end of the spectrum, Figure 2 shows death associated with cerebral angiography to be the most often overestimated of the survey items.

Several factors could help account for the extreme variability of these risk estimates. Current, accurate and consistent data regarding death and complication rates are not easily found in the literature. Personal clinical experience may play a role in causing physicians to underestimate or overestimate complications rates. If one has seen a particular complication only rarely, one may underestimate its general occurrence, while personal experience with a particular complication may lead some physicians to overestimate its rate of occurrence. Regional variations may also exist in rates of complications of these procedures. The most obvious explanation, however, must be that this information is simply not known to these physicians. In ignorance of the published rates, estimates are based on "gut feelings," on personal experience or on some idea of what one thinks the occurrence rates ought to be.

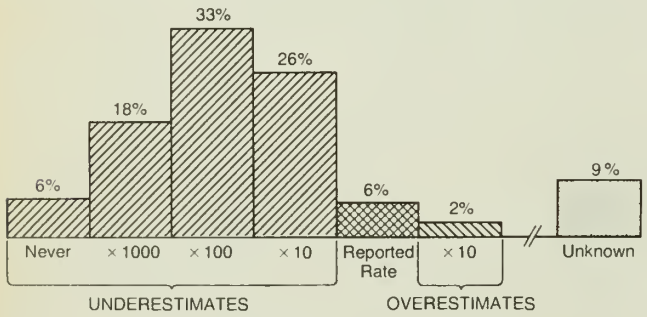

Figure 1.—Estimation of risk of death from herniorrhaphy.

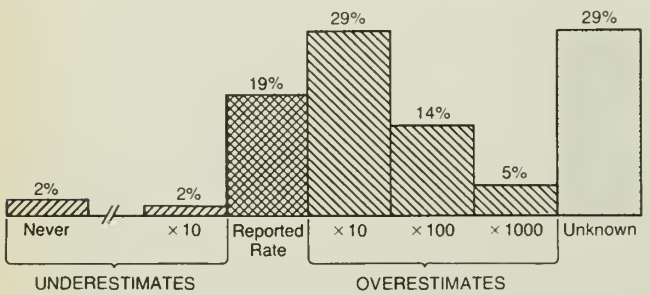

Figure 2.—Estimation of risk of death from cerebral angiography.

It might be argued that physician knowledge is, in fact, accurate and it is the published rates of complications that are in error. It would be highly unlikely that this possibility would apply to ten varied surgical and diagnostic procedures. Published morbidity and mortality rates are usually reported from major clinical centers where complication rates may be lower than in general.[33] Reports may also be more likely to come from those authors who find their experience superior to that previously published. These effects might make the published rates relatively low compared with the general experience in the respondents' communities. If so, such effects would tend to obscure true underestimation errors and exaggerate true overestimation errors apparent in our data. More fundamentally, the extreme variability of estimates made by physicians—sometimes spanning several orders of magnitude—itself shows that a substantial proportion of physician estimates must be incorrect regardless of which questionnaire response is considered the accurate rate.

It is possible that some respondents, particularly those who gave very low underestimates of complication rates or who claimed certain complications never occurred, answered with reference to their personal experience rather than to generally reported rates. If so, such physicians must have disregarded or misunderstood the questionnaire instructions. None of the 25 FP/GPs and GSs in our pilot study of the questionnaire made such errors. Also, the likelihood of these gross underestimates was not related to specialty or to whether or not the physician personally carried out the procedure, as would be expected if their reporting of "personal complication rates" was responsible for these errors. Such misunderstandings, if they did occur, would be unlikely to explain the large overestimation errors.

The possible consequences of not knowing this information are readily apparent. If physicians underestimate the risks of a procedure, more patients may be subjected to the procedure with the associated increases in morbidity, mortality and health care costs. It seems likely that if physicians knew that the risk of death among elderly men undergoing herniorrhaphy was actually much higher than they currently estimate, fewer elective hernia repairs would be carried out on such patients. The converse may also apply: if risks are overestimated, we may tip the balance of clinical decision against the use of the procedure, thereby depriving our patients of a valuable therapeutic or diagnostic alternative. The magnitude of some of the commonly made errors in estimating these risks suggests that their effects may be of great clinical significance and have substantial impact on health services.

This study had limitations in scope and design. A relatively small number of physicians in one state were tested on their knowledge of complication rates for only ten procedures. Criticism can always be directed at the standard rates used. Physicians were asked to select among a choice of orders of magnitude and some estimates that were near the borderline between categories may have been misclassified. Assessment of physician knowledge was limited to estimation of the rate of death and specific complications associated with selected procedures. No test was made of other important knowledge such as recognition of common complications, complication prevention and management techniques, or characteristics identifying high-risk patients. The same questions regarding physician knowledge of complication rates can, and should, be asked of medical therapies.

The questionnaire return rate of 46% requires consideration of nonresponse bias and caution in generalizing these results to all physicians. Study physicians were drawn randomly from the Washington State Medical Association membership, a group which includes 75.2% of all physicians licensed in the state and has been shown to be demographically representative of all nonfederal physicians practicing in the state. In order to guarantee true anonymity to the respondents, the study design forfeited the opportunity to identify nonrespondents and therefore no formal comparison can be made between the two groups. The fact that the questionnaire response rate was equal between GSs and FP/GPs suggests systematic nonresponse bias was unlikely. In addition, if nonresponse bias were present, it seems that the respondents would likely be those physicians who believed their knowledge was accurate regarding surgical complication rates. Thus, assuming physicians were generally correct in this self-assessment, the effect of such a bias would be that respondents' knowledge might be more accurate than that of nonrespondents and the study results would underestimate the degree of physician ignorance of these rates.

FP/GPs and GSs appear similarly ignorant of the rates of these risks. Those physicians who carry out invasive procedures must improve their knowledge in this area if they are to make, and help their patients make, informed decisions. Among the physicians surveyed, spanning ten procedures and 20 complications rates, accurate knowledge of the death rate associated with tonsillectomy by those physicians who did tonsillectomies was the only association found between performance of a procedure and knowledge of its risks. If family physicians and other primary care physicians are to make appropriate referrals and provide their patients with guidance in choosing and consenting to surgical or diagnostic procedures, they must accept the responsibility for acquiring the requisite knowledge of the attendant risks. It would be unreasonable, unnecessary and impractical to inundate ourselves in a sea of numbers attempting to memorize the rates of every complication of every procedure. Rather, each of us must know the important risks and their approximate rates for those procedures we personally carry out. In addition, we should be familiar with the risks and their rates for procedures used in the diagnosis and treatment of those conditions we treat as primary or consultant physicians. This educational process needs to begin in residency and continue throughout one's career in order to keep the information current with advances in practice. Only with accurate information on the risks of the procedures we use can we bring to the care of our patients the responsibilities of a physician—as surgeon, teacher and advisor.

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Problems Experienced by Residents in Internal Medicine Training

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A review of the literature and the experience of a residency program in internal medicine indicate that house officers have special problems during training. Some are shared by all residents, whereas others are unique to certain groups. These problems are caused by historical and cultural factors that have led to the current structure of many residency programs and often interfere with the parallel development of professional, personal and family growth. Program directors and chiefs of service need to be flexible and humane and should negotiate clear expectations with house staff to allow efficient functioning of the residency program and insightful personal growth.

Wolfe ES, Jones HW III: Problems experienced by residents in internal medicine training [Medical Education]. West J Med 1985 Apr; 142:570-572)

For the past ten years, the Department of Internal Medicine at the Kaiser-Permanente Medical Center, Santa Clara, California, has had a residency program in internal medicine.[1] Physicians in internal medicine residency programs have special problems that are shared by all residents, but historical and cultural factors alter the impact on different subgroups of residents: women, men, single residents, married residents and physician couples. The proportion of women entering the program has been higher than the national average for almost every academic year (Table 1).[2,3] This high percentage of female residents has enabled us to observe and describe some gender differences in how residents are affected by and respond to certain problems.[4-6] Professional socialization, conflicts between personal and professional commitment, the role of the spouse, pregnancy and sexuality are discussed and illustrated with specific examples. A more insightful understanding of these issues would enable faculty and program directors to be more effective teachers and counselors for residents and for students who plan to train in internal medicine.

Professional Socialization

Residency training is a synthesis leading to new knowledge, skills, values and perspectives that result in the formation of a professional identity. Problems with professional socialization often begin in medical school, when students are exposed to ways to plan for a fulfilling career as a physician. Some traditional mechanisms of coping with the stress of professional life are not suitable for the time of residency.[7] Hostility, cynicism and defensiveness may occur in response to the stress of training and difficulty in using anger constructively. Almost all residents experience anxiety about their clinical performance, and a few are either underconfident or overconfident about their ability.

Men who attempt to emulate a strong masculine role may displace emotions, display a lack of compassion and seem cool and aloof.[7] They are often unconcerned with the effect on their personal development that is mandated by this behavior. Women, too, experience problems during this process, and several factors may lead to difficulties in their creation of a professional identity.[8-10] There have been few women-physician role models, so that women residents compete in a predominantly male domain and are subject to skepticism and criticism from male physicians.[11] Colleagues and supervisors may perceive as "aggressive" behavior that would be considered assertive in a male resident. Women physicians experience another disadvantage when they are in training programs where they have been a rarity in that both patients and hospital personnel confuse them with nonphysician hospital staff and may refer to them as "girls."

Conflicts Between Personal and Professional Commitments

Residency training requires major time and learning commitments; therefore, conflicts inevitably occur between the time and energy needed for personal and for professional de-

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TABLE 1.—*Sex Distribution of PGY-1* Medical House Staff at Kaiser-Permanente Medical Center, Santa Clara, Compared With the National Percentage of Graduating Female Medical Students*

Year	Female (No.)	Male (No.)	Female (Percent)	Female Medical School Graduates† (Percent)
1972	0	3	0.0	9.0
1973	3	2	60.0	8.9
1974	2	5	28.6	11.1
1975	0	6	0.0	13.4
1976	4	3	57.1	16.2
1977	3	3	50.0	19.2
1978	2	6	25.0	21.4
1979	5	2	71.4	23.0
1980	3	4	42.9	23.2
1981	8	0	100.0	24.8
1982	5	4	55.6	25.0
Totals	35	38	Mean= 47.9	Mean=17.8

*Postgraduate year 1.
†From Crowley et al.[3]

velopment. "Role strain" occurs when residents feel guilt and resentment at the demands of hospital responsibilities if personal needs are neglected and they have similar feelings at home if career development seems compromised.[11] Ambivalence and guilt may lead to disruptive or destructive behavior. Some become more nonchalant about training and spend less time at the hospital.

Women residents who strive for this precarious balance between their personal and professional lives have some unique problems. Unmarried residents of either sex may experience considerable social isolation, but these important years of childbearing and motherhood place unusual stresses on women. These additional responsibilities may conflict with professional development and commitment. Coping mechanisms are strained and the stress interferes with personal and professional life.[12-14]

Male residents often are as concerned about family obligations, but women seem more anxious about responsibilities to their spouse and children.[15] Depression commonly occurs when hospital responsibilities interfere with residents' participation in important activities of their children.[16]

Role of a Spouse

An appropriate adjustment of a spouse or close friend to a partner's period of residency is essential to ensure continuing growth of the relationship. Spouses who are supportive are major assets; those with negative patterns of behavior interfere with the educational experience. Physician spouses are usually more empathic, especially if they are occasionally consulted about clinical problems or the training process. A nonphysician spouse is more likely to feel abandoned and to develop feelings of depression, isolation and hostility. A nonphysician husband may react to his wife's professional success with anxiety and loss of self-esteem if he believes he is not embodying a traditional masculine role.[7,11,14] Some husbands have difficulty responding creatively to a need for role redefinition, which leads to less career parity within a marriage. Marriage can be more stressful than nurturing for women.[17]

Illustrative Cases

CASE 1. A female resident had an interpersonal conflict with a male resident. There was a loud argument, which the woman interpreted as belligerent behavior on the part of her colleague. She discussed the problem with her husband, who then threatened the male resident.

CASE 2. The husband of a first-year resident telephoned the program director to complain about his wife's wages. He stated that her annual salary was too low when calculated as an hourly wage.

CASE 3. When it was time to plan schedules for a new academic year, the husband of one of the first-year residents requested that he be allowed to attend planning sessions. He stated that he needed to represent his wife's interest, implying that she was unable to be her own advocate.

CASE 4. This husband demanded that his wife be home by 5 PM on nights when she was not on call, so that she could prepare his dinner.

Pregnancy

Pregnancy during residency training presents specific challenges to program directors and results in unique problems for a resident.[13,18] Scheduling adjustments necessitated by planned pregnancies may cause hardship when responsibilities are displaced to others. Unplanned pregnancies may cause enmity when residents who choose to have abortions are critical of those who choose to go to term. Some program directors expect all women to defer childbearing until completion of training (K. Holub, "Pregnancy Memo Puts Conflict in Open," *San Jose Mercury News*, Aug 30, 1983, p 1). Even when residents carefully plan pregnancies and return to full-time responsibility after a prudent leave, there are problems coping with both the infant and the residency. The impact of a wife's pregnancy on a male resident is not of the same magnitude.

CASE 5. A third-year resident planned a pregnancy during her final year of training. She returned to full-time activity within a short time of the baby's birth. To continue breast-feeding, she brought the infant to the hospital frequently and, on occasion, nursed the baby during conferences. Nonphysician female employees who did not have this privilege expressed resentment about the breast-feeding and complained about the noise made by the infant.

Sexuality

Occasionally specific problems occur in the areas of sexuality. Both men and women residents are subject to sexual harassment and discrimination, but women report more incidents.[19,20] Male and female residents report episodes of sexual dysfunction that they attribute to the physical and mental stress of training.

Some female residents try to integrate themselves into the predominantly male profession by manipulating the way they, themselves, dress or react.[7] Women residents cry more than their male peers. However, crying is an effective way to release emotions that develop when dealing with illness and death and to demonstrate compassion or empathy.[15]

Recommendations

Residents will be more likely to achieve personal and professional goals if they are prepared for the stresses of both

training and clinical practice. Program directors should provide resource information and authoritative counseling. These issues should be discussed in medical school; residency programs would then continue to emphasize this important part of professional development.

Emotional support must be provided in every residency program so that stresses may be easily identified and ameliorated. This support may be offered in different ways. Stress reduction groups, patterned after those developed by Balint,[21] provide a forum to discuss personal and other problems encountered in training. These groups can be effective when led by program directors because of their direct knowledge of the educational program and its stress points. An alternative leader could be a psychiatrist who is well acquainted with the residency program and is sensitive to the needs of residents. Personal counseling by program directors is another effective way to help residents.

Involving spouses and friends in informal activities acquaints them with the vicissitudes of training. A pleasant social gathering early in the academic year provides contact with other spouses and enables networking to begin. The partners should be introduced to the hospital environment and its ambiance. A change in the professional status of either partner requires deliberate planning; a hiatus in the residency need not prevent the eventual completion of training.

Pregnancy during residency necessitates skillful time management. Scheduling a leave of absence before and after delivery requires flexibility within the program and the support of all members of a house staff. Limitations should be discussed and reviewed periodically for appropriate changes (of course, all legal requirements must be followed). Programs should consider accommodating breast-feeding and other important aspects of infant or child care. There will be a continuing need for day care centers and cooperative nursery schools; larger medical centers may want to help in their organization and administration.

Frank discussions about sexual harassment enable residents to express their concerns. An experienced colleague is a useful resource when this issue is discussed.

Conclusion

It is clear from a review of the literature and the experience of this residency program in internal medicine that house officers have special problems during training. Some are shared by all residents, whereas others are unique to certain groups. These problems often interfere with the parallel development of professional, personal and family growth. All physicians should be taught how to link professional and personal growth.

Program directors and chiefs of service need to be flexible and humane and should negotiate clear expectations with house staff to allow efficient functioning of the residency program and insightful personal growth. Attempts to solve these dilemmas by legislation are unlikely to be as successful as the flexibility, ingenuity and awareness of program directors.[22-24]

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Information

Physician Oversupply—The Views of 1,900 California Physicians

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PHYSICIAN SUPPLY has again become a topic of concern within the medical community and among public policymakers. It last received attention during the 1960s when a physician shortage was widely perceived and measures were undertaken to augment the supply of physicians. Growth in physician manpower accelerated rapidly during the ensuing decade, and the primary issue now is not a shortage but the possibility of an oversupply. Fueled by findings of the Graduate Medical Education National Advisory Committee, which forecast a national surplus of 70,000 physicians by 1990,[1] concern about the prospect and potential ramifications of physician oversupply has mounted.

Interest in the issue has been keen in California, where the physician-to-population ratio is among the highest in the nation and where the supply of physicians has expanded more than twice as fast as the population during recent years.[2] In view of the continuing rapid increases in the relative supply of physicians and the lack of substantive information about how physicians themselves view current and projected levels of supply and the potential impact of a physician surplus, we conducted a survey to elicit the perceptions and opinions of practicing physicians on these issues.

Methods

The survey instrument we used was a mailed, self-administered, two-page questionnaire consisting primarily of precoded, fixed-alternative questions but providing for some open-ended responses. The content of the questionnaire was developed through discussions between California Medical Association (CMA) research staff and physician members of CMA's Committee on Physician Supply, and was subsequently reviewed and refined by the association's Bureau of Research and Planning.

Copies of the questionnaire were mailed to a randomly selected sample of 2,822 physicians from among the universe of active nonfederal physician members of CMA engaged in direct patient care activities, representing approximately 10% of total CMA membership. A postcard reminder was sent to all nonrespondents after one month and at the end of two months a second copy of the survey form was mailed to remaining nonrespondents.

(Purdy RJ: Physician oversupply—The views of 1,900 California physicians [Information]. West J Med 1985 Apr; 142:573-577)

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Usable responses were received from 1,900 physicians, a net response rate of 67.3%. Response rates for individual demographic segments of the sample were excellent, and analysis showed the responding sample to closely reflect the geographic and specialty distributions of California's physician population.

Results

Assessment of Current Supply

Asked to assess the adequacy of the current supply of physicians in the immediate geographic area their practice serves, in the county in which their practice is located and in the state as a whole, a majority of respondents indicated that an excess of physicians exists in each of the three geographic delineations (Table 1). However, while the preponderance of respondents throughout the state agreed that there are too many physicians in California, perceptions of local supply varied widely according to practice location and appeared to reflect known disparities in relative supply (that is, physicians per population). The perception of oversupply was most prevalent among physicians practicing in major urban centers, where more than two thirds of respondents deemed both their county and the specific geographic area their practice serves oversupplied. In some large metropolitan area counties the proportions were substantially higher—exceeding 90%, for example,in San Francisco and in the adjacent county of Marin.

Regarding the supply of physicians in their own primary specialty, most respondents considered their fields overcrowded both locally and at the county level (Table 2). Oversupply was most widely perceived among surgeons, a majority of whom also thought there was an excess of co-specialists statewide. Among nonsurgical specialties, dermatology, anesthesiology and pathology were also deemed to have a statewide surplus by a clear majority of practitioners. General/family practice was the only major field in which an appreciable number of physicians believed a shortage to exist, although a majority of respondents nevertheless thought there was an adequate or more than adequate supply.

A tabulation of responses regarding the adequacy of specialty supply according to practice location confirmed that physician crowding is felt most keenly in large metropolitan areas and among surgical specialists (Table 3). With the exception of general and family practitioners, the preponderance of physicians in major metropolitan areas considered their specialties overcrowded in the county where they practice, with the proportion reaching as high as seven in ten among surgeons. Even in the least populated, primarily rural counties, 44.4% of the surgeons thought there were too many surgical specialists in their area.

Recent and Projected Trends in Supply

Consonant with the documented expansion of physician supply in all areas of the state, a uniformly large majority of respondents in each type of geographic area concurred that

the relative supply of physicians in their specialty had increased during the past few years in the geographic area their practice serves. At least 85% of respondents in each major specialty other than general and family practice affirmed such an increase in the physician-to-population ratio; even among general and family practitioners, however, the proportion was a substantial 70%.

With reference to national trends, most respondents agreed that more physicians are entering practice in the United States than are needed to provide an optimal level of care to the population, both in general (64.7%) and in their own specialty (59.6%), although psychiatrists and general and family practitioners did not concur with this overall assessment with respect to their fields. Asked to react to the Graduate Medical Education National Advisory Committee (GMENAC) forecast of a national surplus by 1990 of 70,000 physicians, 37.1% of respondents thought "the figure looks about right," 18.7% believed "the surplus will be even

TABLE 1.—*Perception of the Adequacy of Physician Supply in Various Geographic Areas, by Practice Location**

		Perception of the Adequacy of Physician Supply In—											
		Specific Geographic Area Practice Serves				County in Which Practice Is Located				California			
Practice Location	N	Too Many MDs (%)	About Right (%)	Too Few MDs (%)	Can't Judge (%)	Too Many MDs (%)	About Right (%)	Too Few MDs (%)	Can't Judge (%)	Too Many MDs (%)	About Right (%)	Too Few MDs (%)	Can't Judge (%)
Major metropolitan area†	1,370	69.9	23.5	1.1	5.5	68.6	21.7	1.2	8.5	51.7	25.6	1.2	21.5
Other metropolitan area‡	326	49.7	38.4	6.1	5.8	47.3	41.1	6.1	5.5	53.4	27.0	2.4	17.2
Semiurban area§	84	36.9	56.0	4.7	2.4	47.6	44.0	6.0	2.4	51.2	27.4	1.2	20.2
Primarily rural area‖	58	22.4	58.6	15.5	3.5	15.5	67.2	13.8	3.5	53.4	25.9	...	20.7
State total	1,838	63.3	28.7	2.6	5.3	62.2	27.6	2.7	7.6	52.0	26.0	1.4	20.6

*Excludes 62 respondents (primarily residents) whose practice location is unknown.
†Includes counties in Standard Metropolitan Statistical Areas (SMSAs) with population over 1 million.
‡Includes counties in SMSAs with population of 1 million or less.
§Includes counties with one or more cities over 25,000 but not within an SMSA
‖Includes counties with no city over 25,000 and more than half of population residing in unincorporated areas.
Note: Percentages may not total exactly 100% due to rounding.

TABLE 2.—*Perception of the Adequacy of Specialty Supply, by Specialty**

		Perception of the Adequacy of Physician Supply In Respondents' Specialty in—											
		Specific Geographic Area Practice Serves				County in Which Practice Is Located				California			
Specialty†	N	Too Many MDs (%)	About Right (%)	Too Few MDs (%)	Can't Judge (%)	Too Many MDs (%)	About Right (%)	Too Few MDs (%)	Can't Judge (%)	Too Many MDs (%)	About Right (%)	Too Few MDs (%)	Can't Judge (%)
General/family practice	325	33.5	45.2	18.8	2.5	31.1	44.0	19.7	5.2	24.9	27.4	26.2	21.5
Medical specialties (total)	488	59.8	33.4	3.3	3.5	52.9	34.4	4.9	7.8	39.6	35.2	3.5	21.7
Internal medicine	301	60.8	32.9	3.3	3.0	52.5	34.9	4.3	8.3	37.2	38.2	2.7	21.9
Pediatrics	88	60.2	33.0	4.5	2.3	48.9	37.5	6.8	6.8	34.1	37.5	5.7	22.7
Dermatology	31	58.0	35.5	...	6.5	71.0	25.8	...	3.2	71.0	9.7	...	19.3
Cardiovascular diseases	36	58.3	38.9	2.8	...	52.8	27.8	8.3	11.1	38.9	38.9	2.8	19.4
Other medical specialties‡	32	53.1	31.3	3.1	12.5	50.0	37.5	6.3	6.2	46.9	21.9	9.3	21.9
Surgical specialties (total)	636	68.1	28.1	1.3	2.5	65.5	28.1	1.3	5.0	55.2	24.4	1.9	18.5
General surgery	146	66.4	28.8	2.1	2.7	71.2	21.2	2.8	4.8	61.6	15.8	2.7	19.9
Neurological surgery	25	68.0	24.0	...	8.0	64.0	28.0	...	8.0	76.0	12.0	...	12.0
Obstetrics/gynecology	131	59.5	35.9	2.3	2.3	52.7	39.7	2.3	5.3	35.1	39.7	3.8	21.4
Ophthalmology	82	79.3	20.7	...	...	72.0	21.9	...	6.1	69.5	14.6	...	15.9
Orthopedic surgery	95	67.4	27.4	2.1	3.1	65.3	31.6	...	3.1	54.7	27.4	1.1	16.8
Otorhinolaryngology	41	70.7	29.3	...	...	68.3	24.4	2.4	4.9	43.9	26.8	...	29.3
Plastic surgery	28	85.7	10.7	...	3.6	78.6	17.8	...	3.6	67.9	14.3	...	17.8
Urological surgery	66	75.8	21.2	...	3.0	71.2	22.7	...	6.1	62.1	24.3	...	13.6
Other surgical specialties§	22	40.9	54.6	...	4.5	45.5	50.0	...	4.5	40.9	36.4	9.1	13.6
Other specialties (total)	396	52.8	38.1	5.6	3.5	53.5	38.6	4.1	3.8	45.7	29.6	6.3	18.4
Anesthesiology	94	54.3	40.4	2.1	3.2	54.3	40.4	3.2	2.1	52.1	29.8	4.3	13.8
Pathology	45	66.7	28.9	2.2	2.2	71.1	22.2	...	6.7	71.1	15.6	...	13.3
Psychiatry	87	56.3	29.9	6.9	6.9	55.2	34.5	3.4	6.9	28.7	34.5	9.2	27.6
Radiology	100	51.0	43.0	4.0	2.0	55.0	42.0	2.0	1.0	49.0	34.0	3.0	14.0
All other specialties‖	70	40.0	44.3	12.9	2.8	37.1	47.1	11.4	4.3	37.1	25.7	14.3	22.9
Total, all specialties	1,845	56.5	34.7	5.8	3.0	53.6	34.9	6.1	5.5	43.7	28.9	7.5	19.9

*Excludes 55 respondents whose specialty is unknown
†Listed individually only if 25 or more respondents specified as their primary specialty
‡Includes allergy, gastroenterology and pulmonary diseases.
§Includes colon and rectal surgery and thoracic surgery.
‖Includes emergency medicine, aerospace medicine, general preventive medicine, occupational medicine and the like

greater" and 20.8% indicated they "don't think the surplus will be that great." Only 4.8% said they did not believe there will be a surplus in 1990. (The remaining 18.6% did not express an opinion.) Combining the first two responses, a total 55.8% of respondents believe the GMENAC forecast to be either roughly accurate or understated; including the responses of those who indicated the surplus will be of lesser magnitude than predicted by GMENAC, a full three quarters of the physicians surveyed (76.6%) anticipated a national physician surplus of *some* magnitude by the end of this decade.

Competitive Reactions to Increasing Supply

One section of the questionnaire asked physicians if they had found an increase in competition for patients during the past few years in the geographic area their practice serves. It was conjectured that, although an oversupply of physicians may not result in the price competition observed in the marketplace for other goods and services as supply increases relative to demand, growth in physician supply might nevertheless give rise to other manifestations of competitive behavior. Several ways in which physicians might have become more competitive were listed and respondents were asked to indicate which, if any, they had observed in their own area.

As shown in Table 4, more than four out of five respondents agreed that competition for patients had intensified. Not surprisingly, this perception was most prevalent among surgeons and among physicians practicing in major metropolitan areas—the specialties and locations in which the perception of oversupply was most prevalent. However, even among rural physicians, relatively few of whom considered their area oversupplied, a substantial majority also said that competition for patients had increased. The manifestation most frequently reported among all respondents was "greater willingness to enter into agreements (such as with health maintenance organizations or individual practice associations) to accept payments below 'usual, customary or reasonable' levels." Similarly sizeable and more uniformly observed proportions of respondents indicated that physicians in their area are "accepting referrals from more sources" and "expanding

TABLE 3.—*Perception of the Adequacy of Specialty Supply in County in Which Practice Is Located, by Practice Location**

		Perception of the Adequacy of Physician Supply In Respondents' Specialty Among Physicians Practicing in—															
		General/Family Practice (N=318)				Medical Specialties (N=481)				Surgical Specialties (N=634)				Other Specialties (N=394)			
Practice Location†	N	Too Many MDs (%)	About Right (%)	Too Few MDs (%)	Can't Judge (%)	Too Many MDs (%)	About Right (%)	Too Few MDs (%)	Can't Judge (%)	Too Many MDs (%)	About Right (%)	Too Few MDs (%)	Can't Judge (%)	Too Many MDs (%)	About Right (%)	Too Few MDs (%)	Can't Judge (%)
Major metropolitan area	1,362	34.8	40.9	17.2	7.1	57.3	30.1	2.7	9.9	70.2	24.0	0.8	5.0	62.7	30.1	2.7	4.5
Other metropolitan area	325	27.7	47.0	21.7	3.6	36.9	51.3	10.5	1.3	49.5	43.4	1.0	6.1	29.8	61.2	6.0	3.0
Semiurban area	83	20.0	56.0	24.0	...	60.0	26.7	13.3	...	50.0	45.0	5.0	...	26.1	65.2	8.7	...
Primarily rural area	57	16.7	66.6	16.7	...	20.0	60.0	20.0	...	44.4	44.4	5.6	5.6	16.7	75.0	8.3	...
State total	1,827	31.1	44.7	18.9	5.3	53.0	34.3	4.8	7.9	65.6	28.2	1.1	5.1	53.6	38.8	3.8	3.8

*Excludes 73 respondents whose specialty and/or practice location is unknown
†See footnotes to Table 1 for definitions of areas.

TABLE 4.—*Perception of Whether There Has Been an Increase in Competition Among Physicians for Patients During Past Few Years in Geographic Area Practice Serves, by Type of Specialty and Practice Location*

		Type of Specialty				Practice Location†			
Response	All Respondents* (N=1900) (%)	GP/FP (N=325) (%)	Medical (N=488) (%)	Surgical (N=636) (%)	Other (N=396) (%)	Major Metro. (N=1370) (%)	Other Metro (N=326) (%)	Semiurban (N=84) (%)	Primarily Rural (N=58) (%)
Competition has increased	81.9	76.0	84.0	86.5	80.1	84.4	80.4	76.2	63.8
Forms of competition observed‡									
Charging lower fees	7.2	7.4	3.9	7.1	11.9	8.2	5.5	3.6	5.2
Advertising/public relations	40.5	40.3	37.7	46.7	36.1	44.1	35.6	26.2	19.0
Expanding types of services provided (specialty "turf" invasion)	58.5	50.5	60.0	61.6	60.4	59.6	58.0	61.9	51.7
Accepting referrals from more sources	59.6	48.9	61.9	61.9	63.1	61.3	57.1	57.1	51.7
Accepting categories of patients not previously treated (eg, Medi-Cal, Workers' Compensation, legal consultations)	51.1	44.9	50.2	53.9	55.1	52.9	52.1	42.9	34.5
Greater willingness to enter into agreements (eg, with HMOs or IPAs) to accept payments below usual, customary or reasonable levels	60.6	54.2	61.9	66.7	58.3	66.5	53.4	39.3	24.1
No increase in competition	11.3	19.4	9.4	10.1	10.1	9.4	15.3	19.0	29.3
Unable to judge	6.8	4.6	6.6	3.5	9.8	6.2	4.3	4.8	6.9
Total response	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0

HMOs=health maintenance organizations, IPAs=individual practice associations

*Includes 55 respondents whose specialty is unknown and 62 respondents whose practice location is unknown, not shown separately
†See footnotes to Table 1 for definitions of areas.
‡Respondents were permitted to indicate more than one form of competition.

the types of services provided (that is, specialty 'turf' invasion)."

Two other possibilities listed on the questionnaire—"advertising/public relations" and "charging lower fees"—represent competitive strategies commonly observed in the market for many goods and services, but which have not yet become widespread among physicians. The reported incidence of advertising and public relations activity was greatest in areas with the highest concentration of physicians and most widely perceived by surgeons. Reinforcing the theory that price competition is a relatively inconsequential force in the market for physicians' services, fewer than one in ten respondents in any type of area reported that physicians are charging lower fees.

Effects of Oversupply on Quality and Cost of Care

Asked to assess the impact an oversupply of physicians in their own specialty would have on the quality of medical care, nearly half of all respondents indicated that a surplus would have neither a positive nor a negative effect (Table 5). One in five respondents thought the quality of care would improve, but a significantly greater number—including 43.7% of surgeons—said the quality of care would deteriorate. Most of these physicians agreed that unnecessary procedures would be carried out and about half said that procedures would be done with less proficiency. With reference to cost of care, a plurality of all respondents and a majority of surgeons said charge levels increase as a result of oversupply.

Trends in Workload and Income

To elicit an indication of whether certain socioeconomic characteristics of medical practice may have been affected by expansion in physician supply, respondents who had been practicing in the same community for at least five years were queried about trends in the numbers of patients seen and procedures done during an average workweek and in their income from medical practice. A plurality of all respondents reported no change during the past few years in either the number of procedures or number of patients. Among physicians in general and family practice, however, a plurality in each case reported a decline and relatively few said their workload had increased. Geographically, although a somewhat greater proportion of respondents in major metropolitan areas than in other locations indicated a diminishing patient base, no parallel difference was observed with respect to the number of procedures carried out.

While relatively few respondents reported an increase in their average workload, a plurality (45.4%) said their net income from medical practice had nevertheless risen during the five-year period. As was the case with trends in workload, however, a plurality of general and family practitioners reported a decline. Most respondents observed that their incomes had not kept pace with inflation and had not increased at the rate they had anticipated.

Opinions Regarding Resolution of Manpower Problem

Physicians were divided in their opinions when asked if, in the absence of external mechanisms affecting the future supply of physicians, they thought the forces of supply and demand would be successful in bringing balance to the relative supply of physicians (Table 6). Half of all respondents and more than half of the medical and surgical specialists doubted the ability of the free market to correct a manpower imbalance. Organized medicine and specialty societies, followed closely by graduate and undergraduate medical educators, were the entities most favored to work toward a resolution of the oversupply problem. Among physicians who did express confidence in the self-regulating ability of the marketplace, most agreed it would take longer than five years for supply and demand forces to succeed in correcting an imbalance, and many thought that more than ten years would be necessary.

Respondents were also asked to evaluate ten suggestions for dealing with a physician surplus, whether or not they

TABLE 5.—*Perceived Effects of Physician Surplus on Quality and Cost of Medical Care, by Type of Specialty*

Perceived Effects on—	All Respondents* (N=1900) (%)	Type of Specialty: GP/FP (N=325) (%)	Medical (N=488) (%)	Surgical (N=636) (%)	Other (N=396) (%)
Quality of Care					
Care would improve (total)†	19.8	27.7	21.5	12.3	21.2
Better patient access to physicians	15.5	23.4	17.6	9.9	14.1
More time spent with each patient	15.4	24.3	18.0	9.3	13.6
Care would deteriorate (total)†	31.4	21.8	27.5	43.7	25.8
Unnecessary procedures would be done	28.2	21.2	24.6	40.9	18.9
Procedures done with less proficiency	15.8	7.4	12.5	24.5	13.6
No difference in quality	48.5	50.2	51.0	43.9	52.8
No answer	0.3	0.3	...	0.2	0.3
Cost of Care					
Charge levels increase	45.3	43.4	44.1	51.9	38.6
Charge levels do not change	39.0	37.8	43.0	35.2	40.2
Charge levels decline	14.2	16.9	12.5	10.5	19.7
No answer	1.5	1.8	0.4	2.4	1.5
Total response	100.0	100.0	100.0	100.0	100.0

*Includes 55 respondents whose specialty is unknown, not shown separately

†Since many of the respondents who indicated that care would improve or that care would deteriorate indicated more than one of the listed ways this might occur, the sum of percentages shown for individual ways exceeds totals.

TABLE 6.—*Opinions Regarding the Achievement of Balance in Physician Supply, by Type of Specialty*

Opinion	All Respondents* (N=1900) (%)	Type of Specialty			
		GP/FP (N=325) (%)	Medical (N=488) (%)	Surgical (N=636) (%)	Other (N=396) (%)
Supply/demand forces will work	43.1	49.2	40.6	38.7	47.7
How long it might take†					
Less than 5 years	4.3	4.3	3.9	4.4	5.1
5-10 years	24.1	29.8	21.7	21.2	27.5
Over 10 years	14.1	13.5	14.1	12.7	15.2
Supply/demand forces inadequate	49.9	43.7	52.2	55.2	43.7
Who should intervene‡					
Federal government	17.3	19.1	20.7	17.5	14.6
State government	18.1	18.8	21.9	16.7	14.9
Organized medicine	46.2	41.8	49.2	50.5	40.2
Specialty societies	42.5	30.2	45.1	49.5	38.6
Undergraduate medical educators	35.5	32.0	37.5	38.8	31.1
Graduate medical educators	39.1	33.8	40.8	43.7	33.8
Balance already exists	5.9	5.5	5.1	5.5	8.3
No answer	1.1	1.5	1.8	0.6	0.3
Total response	100.0	100.0	100.0	100.0	100.0

*Includes 55 respondents whose specialty is unknown, not shown separately
†Percentage of respondents who did not specify length of time not shown.
‡Respondents were permitted to indicate more than one alternative.

perceived a present or future manpower problem. Support was particularly strong for four of the suggestions, each of which was deemed a "good idea" or a "fair idea" by three quarters or more of the respondents: "Change immigration policies to limit the number of foreign nationals entering practice in the United States" (90.4%); "Establish some sort of mechanism for evaluating foreign medical schools" (86.0%); "Work within the educational system at the undergraduate level and below to apprise students that opportunities for physicians are limited" (84.6%), and "Tighten licensure requirements in general" (77.2%). Support for these proposals was uniformly high among each of the demographic subsamples.

Suggestions to "voluntarily lower the number of places in US medical schools" and to "lower the number of residency positions" also garnered considerable support; 72.9% and 71.5%, respectively, thought these were good or fair ideas. Opinions were divided in reaction to proposals to "cut back government funds for medical education" and "establish 'certificates of need' by state or area," with nearly equal proportions judging these to be good or fair and poor ideas. Suggestions to "issue licenses by specialty" and "limit the amounts of funding for medical students" were deemed poor ideas by the majority of respondents, although younger physicians were more amenable to the idea of specialty licensure than were their older colleagues.

Conclusion

While an opinion poll of this nature cannot yield a scientific evaluation of either the adequacy of current and projected levels of physician supply or the ramifications of oversupply, the results of this survey nevertheless constitute a reasonably reliable representation of how California physicians view the manpower situation in their profession and the implications of continued growth in the relative supply of physicians. To the extent that competitive trends reported by survey respondents are in fact correlated with expansion in physician supply, and to the extent that opinions regarding the impact of oversupply on the quality and cost of medical care reflect the actual experience of physicians who deem a surplus in their specialty to exist already, these results may prefigure trends likely to become more prevalent as the physician/population ratio continues to climb both in California and nationally. Results of the survey also provide policymakers and planners with an indication of the approaches favored by physicians themselves in any attempt to address physician supply issues.

REFERENCES

1. Graduate Medical Education National Advisory Committee: Final report, Vol 1, DHHS publication No. (HRA) 81-651. Hyattsville, Md, Health Resources Administration, September 1980

2. Bureau of Research and Planning, California Medical Association: Physician supply in California, December 1982. Socioeconomic Report 1984 Sep; 24(No. 6)

In Memoriam

California Medical Association

BREAN, HENRY P., Berkeley. Died January 1, 1985, in Berkeley of a cerebral aneurysm, aged 70. Graduate of Harvard Medical School, Boston, 1943. Licensed in California in 1948. Dr Brean was a member of the Alameda-Contra Costa Medical Association.

DRAKE, WILLIAM E., JR, San Rafael. Died November 16, 1984, aged 57. Graduate of Northwestern University Medical School, Chicago, 1954. Licensed in California in 1957. Dr Drake was a member of the Marin Medical Society.

GARFIELD, SIDNEY R., Oakland. Died December 28, 1984, in Orinda of myocardial infarct, aged 77. Graduate of the State University of Iowa College of Medicine, Iowa City, 1928. Licensed in California in 1930. Dr Garfield was a retired member of the Alameda-Contra Costa Medical Association.

GREEN, ALLAN, Fairfield. Died October 26, 1984, aged 62. Graduate of Yale University School of Medicine, New Haven, Conn, 1948. Licensed in California in 1956. Dr Green was a member of the Solano County Medical Society.

MACDONALD, FRANK A., SR, Sacramento. Died December 22, 1984, in Sacramento, aged 88. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1925. Licensed in California in 1925. Dr MacDonald was a former president of the California Medical Association and a former president and retired member of the Sacramento-El Dorado Medical Society.

MUFF, ANTHONY LIO, Camarillo. Died November 24, 1984, in Santa Rosa, aged 73. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1943. Licensed in California in 1943. Dr Muff was a member of the Ventura County Medical Society.

STANSBURY, ROBERT, Newport Beach. Died November 12, 1984, in Palmdale of complications of cerebrovascular accident, aged 60. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1956. Licensed in California in 1957. Dr Stansbury was a member of the Orange County Medical Association.

STEPHENS, HUGH E., Palm Springs. Died December 6, 1984, in Palm Springs of emphysema, aged 69. Graduate of the University of Kansas School of Medicine, Lawrence-Kansas City, 1940. Licensed in California in 1942. Dr Stephens was a member of the Riverside County Medical Association.

WAGNER, BEVERLY G., Sacramento. Died January 30, 1985, of cancer, aged 71. Graduate of Columbia University College of Physicians and Surgeons, New York, 1950. Licensed in California in 1955. Dr Wagner was a retired member of the Sacramento-El Dorado Medical Society.

WATERS, GEORGE W., San Jose. Died November 25, 1984, in Santa Cruz, aged 76. Graduate of Northwestern University Medical School, Chicago, 1934. Licensed in California in 1935. Dr Waters was a retired member of the Santa Clara County Medical Society.

New Mexico Medical Society

GOODMAN, STEPHEN A., Deming. Died January 18, 1985, in Deming, aged 40. Graduate of Facolta di Medicine e Chirurgia dell'Universita di Bologna, Italy, 1971. Licensed in New Mexico in 1975. Dr Goodman was a member of the Luna County Medical Society.

Utah State Medical Association

BERMAN, HARRY, Salt Lake City. Died January 15, 1985, in Salt Lake City, aged 78. Graduate of the University of Illinois College of Medicine, Chicago, 1933. Licensed in Utah in 1939. Dr Berman was a member of the Salt Lake County Medical Society.

BRIGGS, LELAND STANFORD, Provo. Died January 11, 1985, in Provo, aged 51. Graduate of the University of Utah College of Medicine, Salt Lake City, 1958. Licensed in Utah in 1962. Dr Briggs was a member of the Utah County Medical Society.

CLARK, THOMAS EDGAR, Sandy. Died January 11, 1985, in Sandy, aged 91. Graduate of Jefferson Medical College of Thomas Jefferson University, Philadelphia, 1919. Licensed in Utah in 1920. Dr Clark was a member of the Salt Lake County Medical Society.

DAYNES, BYRON WOODRUFF, Salt Lake City. Died January 18, 1985, in Salt Lake City, aged 76. Graduate of the University of Colorado College of Medicine, Denver, 1936. Licensed in Utah in 1937. Dr Daynes was a member of the Salt Lake County Medical Society.

HOUSTON, VERNON F., American Fork. Died January 20, 1985, in American Fork, aged 87. Graduate of Jefferson Medical College of Thomas Jefferson University, Philadelphia, 1924. Licensed in Utah in 1925. Dr Houston was a member of the Utah County Medical Society.

PEPPER, MILTON, Salt Lake City. Died January 18, 1985, in Salt Lake City, aged 78. Graduate of the University of Colorado College of Medicine, Denver, 1931. Licensed in Utah in 1932. Dr Pepper was a member of the Salt Lake County Medical Society.

SMITH, DAVID EMMANUEL, Salt Lake City. Died November 18, 1984, in Salt Lake City, aged 62. Graduate of the University of Pennsylvania School of Medicine, Philadelphia, 1949. Licensed in Utah in 1950. Dr Smith was a member of the Salt Lake County Medical Society.

Book Reviews

The Western Journal of Medicine *does not review all books sent by publishers, although information about new books received is printed elsewhere in the journal as space permits. Prices quoted are those given by the publishers.*

RECENT ADVANCES IN DIABETES—No. 1—Edited by Malcolm Nattrass, MB, ChB, PhD, MRCP, Consultant Physician, The General Hospital, and Senior Clinical Lecturer, The University of Birmingham, Birmingham, United Kingdom, and Julio V. Santiago, MD, Professor of Pediatrics and Medicine and Associate Director, Diabetes Research and Training Center, Washington University School of Medicine, St Louis. Churchill Livingstone, Inc, 1560 Broadway, New York, NY 10036, 1984. 254 pages, $35.00 (softbound).

Although the editors point out the difficulty in selecting topics in a field in which advances have been as prolific as in diabetes mellitus, they do an extraordinarily fine job.

As a result, there is an excellent balance between the clinical and the scientific which should be attractive to diabetologists, endocrinologists and others with a particular interest in diabetes.

While there is considerable chapter-to-chapter variation in terms of completeness and depth, topics which hold the most interest currently are generally well represented and thoroughly but concisely presented. Bibliographies are up-to-date and useful to the reader who seeks an overview of today's clinical state-of-the-art and research which seems to promise further sweeping changes in diabetes care.

Particularly notable is the editors' goal to bring attention to and stimulate interest in a number of subjects which have not been stressed in the popular literature. Among these are alterations in bone and calcium metabolism in diabetes, the platelet and third phase of coagulation in diabetes and nonspecific glycosylation of proteins in diabetes mellitus.

Other chapters are to be commended. The discussion of exercise in diabetes recognizes the growing awareness of the importance of this factor and explores, albeit briefly, the development of the understanding of the physiology of exercise in health and in diabetes.

Glucose counterregulatory mechanisms also assume increasing importance as efforts are intensified to normalize blood glucose levels. Although many questions remain to be answered regarding these mechanisms, our present knowledge is reviewed with unusual clarity by the author of this chapter.

This is the first volume of a proposed series. If its quality portends that of future editions, we can look forward to a valuable addition to diabetes literature.

ROBERT L. HARE, MD
Portland Diabetes Center
Portland

* * *

ECHOCARDIOGRAPHY—AN INTEGRATED APPROACH—Stephen Arvan, MD, Assistant Professor, Department of Medicine, University of Pittsburgh School of Medicine, and Head, Noninvasive Unit, Montefiore Hospital, Pittsburgh. Churchill Livingstone, Inc, 1560 Broadway, New York, NY 10036, 1983. 503 pages, $60.00.

This book represents an attempt by the author and four contributors to present an "integrated" approach to undersanding clinical echocardiography. In consonance with this approach, the author includes not only high-quality M-mode and two-dimensional echocardiographic examples of normal and abnormal clinical cardiac conditions, but also briefly compares the uses of echocardiography and radionuclide angiography. Furthermore, chapters on cardiac arrhythmias/conduction disturbances and phonoechocardiography feature nice correlations between echocardiography and other noninvasive modalities.

The outline of the book follows a relatively traditional approach, with the first chapter describing the principles of cardiac ultrasound, techniques for performing the echocardiographic examination, standard imaging views and potential imaging artifacts. There is also a brief introduction to Doppler echocardiography. After a brief comparison of echocardiographic and radionuclide techniques in the evaluation of left ventricular function, there are chapters on coronary artery disease, acquired valvular disease, pericardial disease, cardiomyopathy, endocarditis and left ventricular masses. The text in these chapters is well-written and the echocardiographic figures are excellent. The chapter on congenital heart disease is especially useful for cardiologists or internists treating adults who would like a brief illustrative review outlining the major congenital heart diseases. Also, the chapter on prosthetic heart valves provides an excellent reference for those of us involved in interpreting the often confusing and subtle echocardiographic findings on these valves.

In addition to the nice features, there are a few limitations to this book. First, there is no attempt to describe some of the newer, not well-established applications of cardiac ultrasound—such as three-dimensional reconstruction and tissue characterization. Second, the discussion of Doppler echocardiography is rudimentary and outdated. The few Doppler figures included throughout the book were unfortunately produced using older Doppler technology without spectral display. Therefore, these figures cannot give the reader an adequate picture of the information which the Doppler technique currently adds to the ultrasound examination. Furthermore, the author states in his first chapter that "quantitation of flow velocity or volume flow is unreliable" by the Doppler technique. This statement is presumably based on the older technology and does not reflect many recent reports attesting to the utility of Doppler echocardiography for this application. Third, there are only brief allusions to contrast cardiac echocardiography in the book. Finally, the "Table of Normal Values" in the Appendix is apparently based on a small number of subjects and does not give normal M-mode values corrected for age; also, no normal values are included for two-dimensional parameters.

Despite these limitations, I believe that this is a valuable book for those who are interested in the basic principles and clinical applications of echocardiography.

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Medical Centers

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KNEE PAIN AND DISABILITY—2nd EDITION—Rene Cailliet, MD, Professor and Chairman, Department of Rehabilitative Medicine, University of Southern California, School of Medicine, Los Angeles. F. A. Davis Company, 1915 Arch St., Philadelphia, PA 19103, 1983. 177 pages, $11.95.

This is one of a series of books written by Dr Cailliet on the subject of musculoskeletal pain and disability. It is a revision of the first edition, which was published in 1973, and is intended to acquaint nonorthopedic health practitioners with the more common causes of knee problems.

Dr Cailliet is at his best when discussing the structural and functional anatomy of the knee, which takes up the first quarter of the book. The text is easy to read and is aided by a liberal number of clear, schematic drawings. Although recent developments in musculoskeletal biomechanics call into question some

of Dr Cailliet's assertions regarding the functional role of various structures, he is, for the most part, accurate. This section of the book represents a good description of the many components of the knee which, through either dysfunction or injury, can lead to disability.

The rest of the book is composed of a series of chapters outlining the major traumatic, inflammatory, degenerative and neuromuscular affectations of the knee. The chapter on the patellofemoral joint is excellent, explaining the mechanisms by which this structure becomes the most common cause of knee pain. The portion of each chapter pertaining to the rehabilitation of disabled knees is also quite good, reflecting Dr Cailliet's vast experience as a recognized rehabilitation expert.

The sections on diagnosis and treatment are of more variable quality. It is a bit disappointing that many of the advances of the last ten years are not included here. Nowhere is mention made of the proper significance of the acute hemarthrosis, now recognized to be highly correlated with anterior cruciate ligament tears and osteochondral fractures. The Lachman test—the most sensitive physical diagnostic sign of anterior cruciate ligament integrity—is not described. There are occasional other instances where salient points of diagnosis are overlooked or misstated.

Treatment is similarly presented in an outdated manner. Dr Cailliet states that his goal is not to discuss the details of definitive treatment, but much of the text is devoted to this. Perhaps it would be best to have omitted this completely rather than present it inaccurately. His description of the treatment of fractures about the knee is unchanged from the first edition, detailing techniques no longer used. The arthroscope has become a primary tool in the diagnosis and treatment of intra-articular pathologic processes, and is not mentioned. In discussing rheumatoid arthritis, Dr Cailliet states that, "Total knee replacements have not been proven in the number done and duration of their use to be recommended." While possibly true in 1973 (the same quotation appears in the first edition), this is clearly not the case now.

It is indeed difficult to write a specialty book intended for nonspecialists. The tendency is to either include too many details for the general audience or to make too superficial a presentation, risking accuracy. As an introductory text for those unfamiliar with the knee, this book can be conditionally recommended for the purpose of acquainting them with the anatomic structures and diagnostic possibilities. However, it cannot be recommended for those who wish a current, concise discussion of the knee in a single source.

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* * *

HIRSUTISM AND VIRILISM—PATHOGENESIS, DIAGNOSIS AND MANAGEMENT—Edited by Virendra B. Mahesh, Regents' Professor and Chairman, and Robert B. Greenblatt, MD, Professor Emeritus, Department of Endocrinology, Medical College of Georgia, Augusta. John Wright • PSG Inc., 545 Great Road, Littleton, MA 01460, 1983. 394 pages, $49.50.

This book deals with common and rare androgenizing disorders of women and children. These disorders may be managed by various specialists, including endocrinologists, gynecologists, dermatologists and geneticists. It has much to offer.

In the past few years, there has been considerable advance in understanding the biochemical mechanisms involved in hirsutism and virilism. Knowledge of the physiology of gonadal differentiation, sex-steroid secretion and metabolism in various target tissues and sex-steroid receptor interaction that produce biochemical responses has increased considerably. Much of this new information has been extrapolated to explain the pathophysiology of hirsutism and virilism in women and children. The primary biochemical defect for the common causes of hirsutism—polycystic ovary disease and idiopathic hirsutism—are poorly understood. These disorders probably represent a group of various defects with a common clinical expression. The authors of these chapters clearly struggled with the current lack of a satisfactory explanation of the pathophysiology. The biochemistry of the excess hair growth can be explained quite well in these patients from what is known about sex-steroid metabolism and androgen action. What is poorly explained is why these patients produce excess androgens or respond to them excessively. In general, the areas of controversy are carefully outlined and satisfactorily discussed.

There are some errors in the book and some new areas of knowledge that have been omitted. In the chapter on Cushing's syndrome, for example, there are misstatements about factors that modify the metabolism of dexamethasone. It is stated that dexamethasone suppression tests may give abnormal findings in obesity because the clearance of dexamethasone is increased in obesity and the plasma half-life of the steroid is reduced. Extensive experience and published data do not support this statement. Also, the statement that estrogen therapy increases the metabolism of cortisol and dexamethasone is incorrect. The book is devoid of data on newly described androgen markers of hirsutism: plasma 3α-androstanediol and 3α-androstanediol glucuronide.

There are also some oversights in the book. The metabolism of sex steroids in skin and hair follicles is not covered satisfactorily. Data on receptor characteristics of hair follicles and various regions of skin should be covered as a single topic. Information on the incidence of hirsutism and virilism in various populations is also not discussed in any detail. The book could be improved by discussing practical approaches to evaluation of many of the disorders described. The approaches presented are mainly at the level a specialist could interpret, but not a generalist.

Despite these limitations, the book will make a substantial contribution as a reference source for medical students and housestaff who care for patients with these disorders. The authors have many years of experience in managing patients with these disorders and have made numerous contributions to the literature on these subjects. It will be a welcome addition to medical school libraries and the libraries of endocrinologists, dermatologists and those physicians in obstetrics and gynecology and pediatrics who care for patients with disorders of either hirsutism or virilism.

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* * *

PEDIATRIC EPILEPTOLOGY—CLASSIFICATION AND MANAGEMENT OF SEIZURES IN CHILDREN—Fritz E. Dreifuss, MD, FRCP, FRACP, Professor of Neurology, School of Medicine, University of Virginia, and Director, Comprehensive Epilepsy Program, Charlottesville. John Wright • PSG, Inc, 545 Great Rd, Littleton, MA 01460, 1983. 295 pages, $35.00.

The text is a collection of treatises incorporated within 295 pages. More than half of the chapters are written by the editor, Fritz E. Dreifuss. Information is organized into three subject areas. The first three chapters serve as an introduction covering classifications of seizures, a brief description of the genetics of epilepsy and a review of electroencephalographic findings in seizures and epilepsy.

Since 1964 a vigorous international effort has been made to develop an acceptable classification of seizures. The classification is based upon seizure type—that is, partial, generalized and unclassified with subsets of those major categories. The seizure types are separated by their clinical expression, characteristic electroencephalographic findings and, to a lesser extent, site of origin. The latter is much more difficult due to the lack of knowledge regarding the functional anatomy of the brain.

The chapter on the genetics of epilepsy shows the powerful influence of inheritance upon the occurrence of seizures. Study of the genetics of epilepsy is hampered by absence of gene, protein or enzyme markers to follow transmission of the trait through a family.

Dr Soo K. Kee provides a remarkably concise description of the electroencephalographic characteristics of seizures and epilepsy.

The second area of subject material describes, in 11 chapters, the individual seizure types—that is, absence, generalized tonic-clonic seizures, infantile spasms, myoclonic seizures, Lennox-Gastaut syndrome, partial seizures (simple and complex), neonatal seizures, sensory-evoked seizures and status epilepticus. The authors strive mightily to clearly differentiate among the seizure types, especially partial seizures, absence, myoclonic and infantile spasms. This is a difficult task because these seizure types are

heterogenous groups of similar seizure behaviors and even the sophistication of modern clinical studies and electroencephalograms does not always coincide with the clinical expression of the seizure.

Throughout, each author repeatedly emphasizes the absolute need for a careful clinical evaluation, including an accurate history and a step-by-step review of the observed seizure activity followed by a detailed neurological evaluation. In complicated cases, an electroencephalogram can profitably be combined with television monitoring.

The chapters contain excellent and concise comparative tables guiding the reader in, for example, the comparative features of absence seizures and complex partial seizures, comparison of jitteriness and seizures in the neonate and risk factors in febrile seizures. These and many other tables are well described in the text.

The third subject area covered in the last four chapters describes the treatment of an individual with a seizure disorder, including pharmacologic and surgical management, community support systems and psychosocial considerations.

An outstanding chapter by Dr J. Chris Sackellares describes the pharmacologic management. This author provides a general description of drug therapy including toxicity and pharmacokinetics and then addresses the use of each anticonvulsant drug including indications, dosage, time of administration, levels and interactions among antiepileptic agents. This author and others in the text make a strong plea for specific single drug use and avoidance of "polypharmacology."

In the last two chapters, the authors describe community support systems and the impact of a dramatic disorder upon the lives of a patient and family.

This is an excellent book containing information essential to those managing seizures in childhood. Though the information is available in the literature, these authors have incorporated an enormous amount of data in this slim volume. In addition, the authors have paid tribute to investigators from the past such as Hughling Jackson, Penfield and Jasper, Gibbs and many others who contributed so much to our current level of understanding, thus providing a nice historical tie between the past and present. Moreover, the editorial style is clear and concise—perhaps reflecting the traditions found in an editor-neurologist trained at the National Hospital Queens Square, London.

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* * *

THE SEVERELY INJURED LIMB—Christopher E. Ackroyd, MA, MB, BChir, FRCS, Consultant Orthopaedic Surgeon, Southmead General Hospital, Bristol, and Brian T. O'Connor, MS, MChOrth, FRCS, FRACS, Robert Jones Professor of Orthopaedics, Robert Jones and Agnes Hunt Hospital, Oswestry, Shropshire, England, and Pieter F. de Bruyn, FRCS, Consultant Orthopaedic Surgeon, Tiel Hospital, Tiel, The Netherlands. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1983. 258 pages, $44.00.

Badly traumatized extremities present a major challenge, for their proper management revolves not only around assurance of limb viability, but also restoration of as much function as possible. Thus, the mission of Ackroyd, O'Connor, Jones and de Bruyn—to provide up-to-date principles *and* practice for the management of extremity trauma—is timely. Have they met their goal?

The Severely Injured Limb expands upon topics presented at a symposium held in the United Kingdom in 1982. Twenty-two authorities, primarily from Great Britain and the Continent, with contributions from Ehanire of Nigeria and the redoubtable microsurgeon Owen of Sydney, participated, and they have covered the gamut from orthopedics through vascular, plastic and trauma surgery. The book is obviously British, as are most of the references, and American readers' delight with the characteristic British wit and expository elegance ("The only safe place for muscle that does not bleed, nor twitch when pinched, is in the bucket.") may be diminished by the presence of allusions (the Pobble; the Moorgate disaster) meaningless to most on the west side of the Atlantic. The book suffers from unevenness; it begins with a first-rate section on general principles of evaluation, the setting of priorities, what to do with the unreconstructible limb, and the importance of a "team approach." However, it then degenerates into a series of short anecdotal chapters, fully a third of the book, on internal and external fixation of fractures. A high point is again reached with a discussion of injury severity scores, ischemic contracture and the microsurgeon's role in extremity trauma, but the book then goes on to end somewhat lamely with topics, seemingly non sequiturs, on osteomyelitis and the penetration of bone by antibiotics.

This was a "nice try," and could have succeeded brilliantly with some tight editing. The definitive text on badly damaged limbs remains to be written. The importance of the topic, however, warrants this book's presence on the shelves of trauma center libraries.

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MEDICAL ECONOMICS ENCYCLOPEDIA OF PRACTICE AND FINANCIAL MANAGEMENT—Edited by Lawrence Farber, West Coast Financial Editor, *Medical Economics*. Medical Economics Books, Box C-779, Pratt Station, Brooklyn, NY 11205, 1985. 1,253 pages, $69.95 plus a $1.50 handling charge.

This encyclopedia is a remarkable compilation of more than 50 years of actual experience in the business side of the medical profession by the staff of the premier magazine in practice and financial management for physicians.

The book is in two parts. Part one comprises 14 chapters subdivided into some 110 major sections covering every aspect of practice management in depth. It begins with a thorough review of the problems of starting a practice and works all the way through into reviewing future trends that may affect the practice. Between these two extremes it covers the entire range of money, facilities, equipment, personnel and liability, to mention a few. Part two, comprising eight chapters (60 major sections), treats the management of doctors' financial affairs in the same thorough fashion.

This well-written and edited encyclopedia belongs in every hospital and medical school library. To the best of my knowledge there has never been another published work that is as comprehensive and authoritative. It is an excellent reference book covering most of the major decisions that have to be made by a physician. This covers both practice and finances.

Some doctors may even like the encyclopedia for their own personal home library. This gives them a comprehensive book to answer professional or financial problems in the quiet of their own studies.

RICHARD V. BIBBERO, MBA, CPBC
Petaluma, California

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THE DOCTOR'S COMPUTER HANDBOOK—Peter J. Fell, MD, general practitioner in Deddington, Oxford, England; and William D. Skees, President of Skees Associates, Inc, Alexandria, Virginia, an automation consulting firm. Lifetime Learning Publications, Ten Davis Drive, Belmont, CA 94002, 1984. 268 pages, $27.50.

When medical computing applications in the physician's office were limited to what could be done with large ("main frame") computers or even the relatively expensive minicomputers, and the custom programs that operated with them, there was no need for the kind of literature this book represents. The microcomputer ("personal computer") has changed all this. By bringing the cost of computing down to the point where any interested physician could entertain the possibilities of (1) developing his or her own office system, (2) acquiring an inexpensive commercially available system or (3) some combination of the two, there has been a widespread need for an appropriate literature.

Since microcomputers arrived on the scene, this literature was not long in coming. Many of the first books to appear were, unfortunately, disappointing. Several books that appeared quickly had been obviously written in haste, in the hope of reaching the market first. There has also been a flurry of magazines and journals directed to practicing physicians interested in computing. These too have suffered from a great unevenness in quality and competence. In a field with a genuine shortage of experts, there has been no shortage of free-lance writers who, with no particular experience in the field, have not hesitated to act as experts.

The *Doctor's Computer Handbook* by Fell and Skees is an improvement upon most of its predecessors, and although it contains much information that is of an ephemeral nature, a considerable amount will be of permanent value. A great difficulty in writing a book of this type is deciding which issues are worth bothering a physician-reader with, and which are not. I believe the authors have done quite well here. They have wisely avoided a lot of discussion on "bits and bytes," electronic minutiae, and have omitted unessential detail about digital logic and like matters. Instead, they have addressed such important issues as the cost of small computing installations, the difficulties, and risks and benefits of attempting to computerize office procedures, with some solid advice on what to do and not to do.

Dr Fell is a general practitioner in England, where he has developed a "computerized practice," according to the dust jacket, and Mr Skees is an experienced computer professional. The book is surprisingly up-do-date for

one appearing in 1984—a year of rapidly breaking developments in the microcomputer field. For example, it discusses the influential role of the IBM/PC, and it appropriately does not mention the Osborne computer.

No book, to my knowledge, will satisfy all the needs of a physician who may wish to enlarge a suddenly awakened interest in medical office computing. This one, however, does contain a wealth of factual material and many useful references to the relevant literature, all of which is apt to prove handy. I believe the buyer will get his money's worth, especially if this is the buyer's first book on this subject.

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MANAGEMENT OF WILDERNESS AND ENVIRONMENTAL EMERGENCIES—Edited by Paul S. Auerbach, MD, Assistant Clinical Professor of Medicine, University of California, San Francisco, and Attending Physician, Emergency Services, San Francisco General Hospital; and Edward C. Geehr, MD, Assistant Clinical Professor of Medicine, University of California, San Francisco, and Medical Director of Emergency Medical Services, City and County of San Francisco. Macmillan Publishing Company, 866 Third Ave, New York, NY 10022, 1983. 656 pages, $68.00.

This is an extremely authoritative text for medical personnel with an interest in wilderness and environmental emergencies. The editors have sought contributions from experts in each of 21 separate areas which encompass most of the growing field of wilderness and environmental medicine. Specific topics include high altitude illness, diving and barotrauma, hazardous marine life, arthropod envenomation, venomous snake bites, aerospace medicine, heat illness, hypothermia and cold injury, among others. Pathology, case histories, emergency and definitive care are all carefully considered. The physiology, biology and geography are noted when appropriate, specifically for biologic toxins including plants, animals, arthropods and marine envenomations. The chapters regarding wilderness rescue, disaster planning and forest fires include descriptions of the current terminology and delineation of the most recent equipment, resources and management strategies pertinent to these developing areas.

The book is the definitive text in this new and growing area of wilderness and environmental emergencies and should be on the shelf of all physicians and other medical personnel with an interest in this area. It will also be of great interest to nonmedical personnel who are significantly involved in outdoor activities including mountain climbers, serious cross country skiers, scuba divers and rescue personnel. This is the first serious attempt to combine in one volume the medical knowledge relevant to wilderness and environmental medicine. It is a comprehensive guide to an unusual and exciting new area of medicine and includes excellent photographs, tables, graphs and diagrams. It is extremely well written.

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* * *

IMMUNOLOGY OF PARASITIC INFECTIONS—Second Edition—Edited by Sydney Cohen, CBE, MD, PhD, FRCPath, FRS, Head, Department of Chemical Pathology, Guy's Hospital Medical School, London; and Kenneth S. Warren, MD, DTM&H, Professor of Medicine, New York University School of Medicine, Adjunct Professor, Rockefeller University, and Director for Health Services, The Rockefeller Foundation, New York. Blackwell Scientific Publications, 1982. USA Distributor: Blackwell Mosby Book Distributors, 11830 Westline Industrial Drive, St Louis, MO 63141. 848 pages, $96.00.

A better understanding of the immunology of parasitic infections could lead to techniques for eradication of the heavy parasite burden borne by residents of most of the third world and offer models for improved understanding of host responses to other (nonparasitic) diseases. Unfortunately, with a few notable exceptions such as the pioneering work on the immunopathology of tubercle formation in schistosomiasis, until recently the immunology of parasitic infections has been ignored. Investigators working with high-powered research tools to study immunologic processes were rarely knowledgeable about parasitic diseases, and those with clinical or laboratory expertise in parasitology were rarely conversant with modern concepts of immunology or its research techniques. (Less than ten years ago I reviewed a research proposal by a well-known immunologist to study gut immunity by using *Ascaris lumbricoides* in a rat model. Questions of host specificity aside, the applicant seemed totally unaware of the relative size of an adult *Ascaris* and the rat intestinal lumen.)

To foster interaction between parasitologists and immunologists, this book was first published in 1976. This second edition, published in 1982, dramatically illustrates the rapid changes in the knowledge base since 1976. Nearly a fourth of the earlier edition was devoted to immunodiagnosis. The new edition has almost twice as many pages, and immunodiagnosis takes its place along with immunity and immunopathology as the central theme and longest part of the book. The last two chapters offer a remarkably concise synopsis of protozoa and helminths. The book is very nicely printed and well referenced. Experts from several countries concisely and clearly describe the pathogenic mechanisms, host responses and experimental models for 14 protozoal and helminth infections. Newer biochemical techniques have led to the recognition of different species of morphologically similar parasites, leading to the rewriting of much that was said earlier about the epidemiology and pathogenic potential of these parasites. Although improved techniques for characterization of parasite antigens and for the study of host responses have been applied to diverse parasites to good advantage, gaps in understanding remain large.

This book is highly recommended to those interested either in parasitology or immunology. One hopes that the audience for the third edition will be larger.

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FORENSIC MEDICINE: A Guide to Principles—Second Edition—I. Gordon MB, ChB, FRSSAf, Hon MD(Natal), HonLL D(S.A.), Emeritus Professor of Forensic Medicine, University of Natal, and Formerly Chief Government Pathologist, Durban, and Dean, Faculty of Medicine, University of Natal, 1955-1971; H.A. Shapiro, PhD, MB, ChB, FRSSAf, Hon LL D (Natal), Professor of Forensic Medicine, University of South Africa, Visiting Professor of Forensic Medicine, University of Natal, Former Government Pathologist, Cape Town. Churchill Livingstone, Inc, 1560 Broadway, New York, NY 10036, 1982. 451 pages, $50.00.

Few complete and current textbooks on forensic medicine exist. Most of the current information is in the journals, and most of the textbooks are from countries other than the United States. Most of these build heavily on archaic, inaccurate and misleading information, As such they are not suitable reference books for physicians new to the speciality or for physicians who need occasional information in their practices. This is true because persons may lack the necessary depth of background or training to sort out fact from inaccuracy.

This book, *Forensic Medicine: A Guide to Principles*, is a text not to be used by those inexperienced in forensic medicine. it contains many excellent sections which represent authoritative information consistent with the best current medical knowledge. The chapter on postmortem changes is quite good. However, it describes the sexual asphyxia as a suicide and reflects on sudden infant death syndrome (SIDS) more as an accidental asphyxia than a natural death.

There are many examples of case experience that are unique and helpful, so that this would be a beneficial additional reference for the physician working routinely in forensic medicine but not for the primary reference work in the field.

The references generally are remote, with recent citations added to the text. The photographs are of poor quality because of the printing and paper which combine to detract from their illustrative value.

In summary, this is a less than authoritative book, filled with much misleading information and is not recommended for the occasional reader. However, there are excellent sections if one has the primary expertise to make that differentiation. Practitioners of forensic medicine should have this text; others should not make the purchase.

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NEVADA STATE MEDICAL ASSOCIATION
1985 ANNUAL CONVENTION & SCIENTIFIC SESSION

May 9-12, 1985 □ Hyatt Lake Tahoe □ Incline Village, NV

SCIENTIFIC SESSION

Friday, May 10

Program Chairman: John J. Stapleton, M.D.

8:00 am **Introductions**
Anton Sohn, M.D.
President, Nevada State Medical Association

8:15 am **"Surgical Management—Breast Carcinoma"**
James E. Goodnight, M.D., Ph.D.
U.C. Davis Medical Center

9:00 am **"Chemotherapy—Breast Carcinoma"**
Richard J. Cohen, M.D.
U.C. San Francisco School of Medicine

9:45 am Questions & Answers—Panel
Drs. Goodnight and Cohen

10:00 am Refreshment Break

10:15 am **"Corneal Complications of Extracapsular Cataract Extractions and Intraocular Lens Implantation"**
Robert G. Webster, M.D.
Pacific Medical Center, San Francisco

11:00 am **"Breast Reconstruction"**
Stephen J. Mathes, M.D.
U.C. San Francisco School of Medicine

11:45 am Questions & Answers—Panel
Drs. Webster and Mathes

12:15 pm Luncheon and presentation with NSMA Auxiliary
"Stress and the Physician"
G. Douglas Talbott, M.D.—Medical Association of Georgia

1:30 pm **"Overview—Breast Carcinoma"**
Panel: *Drs. Cohen, Goodnight, Mathes*
Moderator: *H. Treat Cafferata, M.D.*

3:00 pm Adjournment

CONVENTION SCHEDULE

Thursday, May 9

4:00 pm NSMA Council Meeting
6:00 pm Reception & Dinner for Council members & wives/guests

Friday, May 10

7:30 am Continental Breakfast
8:00 am Scientific Session
8:00 am Auxiliary Board Meeting
9:00 am Auxiliary Membership Meeting & Workshops
12:15 pm Joint Luncheon
1:30 pm Scientific Session & Auxiliary Workshops continue
3:00 pm Adjournment of Scientific Session
3:30 pm House of Delegates—Opening Session
5:30 pm Cocktail Party

Saturday, May 11

7:30 am Continental Breakfast
8:00 am Reference Committees
Auxiliary Workshops
Noon Lunch & Afternoon Activities—on your own
4:00 pm Nevada Chapter of American College of Surgeons—Committee on Trauma
6:00 pm Presidents' Inaugurations & Awards Ceremony—Wine served
7:30 pm Bavarian Bierstube—Relax, Dine, Dance & Sing in the Atmosphere of a Bavarian Beirhall!

Sunday, May 12

7:30 am Continental Breakfast
8:00 am House of Delegates—Closing Session
11:00 am Adjournment

HEADQUARTERS HOTEL

THE HYATT LAKE TAHOE—Majestic High Sierras, towering pines, crystal clear waters and spacious, elegant sleeping rooms overlooking Lake Tahoe at Incline Village, Nevada. You'll discover an indoor health spa, outdoor heated pool, and an 18-station exercourse in the pine forest adjacent to the hotel. Selection of fine restaurants including Hugo's Rotisserie.

REGISTRATION

Name _____

Address _____

City/State/Zip _____

Telephone _____

Return this form along with appropriate fees to the Nevada State Medical Association, 3660 Baker Lane, Reno, NV 89509, or register by phone, (702) 825-6788, Kathleen Boyce, Convention Manager. Housing information will be forwarded upon receipt of registration.

CHECK ONE:	Before May 1	After May 1
NSMA Members		
(General Registration)		
Regular	$150	$160
Out-of-state	100	110
Retired	75	85
Resident	75	85
Student	50	60
Nonmembers		
(Scientific Session only)		
Physicians	$150	$160
Nurses	50	60

Scientific Program

Acquired Immune Deficiency Syndrome (AIDS)
Contemporary Issues in Medical Ethics
Nuclear Magnetic Resonance

Accreditation

As an accredited organization for continuing medical education, the New Mexico Medical Society certifies that this educational offering meets the criteria for 9 credit hours in Category I of the Physicians Recognition Award of the American Medical Association. It is acceptable for 9 prescribed hours, AAFP.

WEDNESDAY, MAY 1

8:30 AM	NM Physicians Mutual Liability Company—Board of Directors Meeting
10:00 AM	Registration
10:30 AM	NM Physicians Mutual Liability Company—Annual Meeting
2:00 PM	House of Delegates—First Meeting Guest: Alan R. Nelson, MD, Trustee, Board of Trustees, American Medical Association
3:30 PM	Reference Committee Hearings
6:30 PM	President's Reception and Banquet

THURSDAY, MAY 2

ACQUIRED IMMUNE DEFICIENCY SYNDROME (AIDS)

Presiding William Boehm, MD, President-Elect, NMMS
Moderator Toby Simon, MD

8:30 AM	**Virology**—Gregory Mertz,MD
9:00 AM	**Pathogenesis of Immune Deficiency**—Darwin L. Palmer, MD
9:25 AM	**Clinical Aspects: Diagnosis and Patient Management**—Donald Romig, MD
10:00 AM	**Refreshment Break**
10:30 AM	**Public Health Implications in New Mexico**—Harry Hull, MD
10:50 AM	**Implications for Blood Donors and Recipients**—Toby Simon, MD
11:10 AM	**AIDS and the Gay Man: Fear and Action in the '80s**—James Waltner, MD
11:35 AM	**Ethical Implications of AIDS**—Ronald A. Carson, PhD

ANNUAL MEETING

MAY 1-3, 1985
ALBUQUERQUE, MARRIOTT HOTEL

THURSDAY, MAY 2, CONTINUED

CONTEMPORARY ISSUES IN MEDICAL ETHICS

Presiding Edward L. Johnson, MD, Vice-President, NMMS

Moderator Robert C. Derbyshire, MD

2:00 PM **Current Problems Related to Medical Ethics**—Ronald A. Carson, PhD

2:45 PM **Case Presentation #1**—R. C. Derbyshire, MD

3:05 PM **Refreshment Break**

3:35 PM **Case Presentation #2**—Alice M. Luna, MD

4:00 PM **Panel Discussion** (written questions from both sessions)
R. A. Carson, PhD; D. L. Palmer, MD; H. Hull, MD; D. Romig, MD; Chas. Leonard, MD; Toby Simon, MD; A. M. Luna, MD; Jas. Waltner, MD; Gregory Mertz, MD, and R. C. Derbyshire, MD, Moderator

6:30 PM Past Presidents Club Banquet
Specialty Society Meetings

FRIDAY, MAY 3

NUCLEAR MAGNETIC RESONANCE

Presiding W. Marion Jordan, MD, President, NMMS

Moderator Charles M. Thompson, MD

9:00 AM **Introduction**—Charles M. Thompson, MD

9:05 AM **The Physics of Nuclear Magnetic Resonance**—William Thompson, MD

9:35 AM **Clinical Applications of NMR**—James L. Lowry, MD

10:05 AM **Refreshment Break**

10:35 AM **Future Possibilities of NMR in Clinical Diagnosis**—William Thompson, MD

11:15 AM **Panel Discussion**
W. Marion Jordan, MD; James L. Lowry, MD; William Thompson, MD, and Charles M. Thompson, MD, Moderator

12:30 PM NEMPAC Luncheon—Classic Hotel

2:00 PM House of Delegates Second Meeting

(Continued on page 586)

(Continued from page 585)

Educational Objectives

This course is designed to provide a review of current management techniques in the diagnosis and treatment of AIDS. It focuses on the social and ethical issues in the practice of medicine today. The presentation of case histories will be followed by a panel where there will be the opportunity for discussion of problems with speakers.

The symposium on nuclear magnetic resonance is oriented to physicians as a brief course on the clinical applications, diagnostic possibilities and the physics of this new technology. A panel discussion will follow.

FACULTY

Ronald A. Carson, PhD
Professor & Director, Institute for Medical Humanities, University of Texas, Medical Branch, Galveston, Texas

R. C. Derbyshire, MD
Surgeon, Emeritus, Retired Secretary, New Mexico Board of Medical Examiners, Santa Fe, New Mexico

Harry Hull, MD
Epidemiologist, New Mexico Department of Health & Environment, Santa Fe, New Mexico

W. Marion Jordan, MD
President, New Mexico Medical Society, Private Practice-Radiology, Albuquerque

Charles Leonard, MD
Private Practice, Nephrology, Attorney at Law, Albuquerque

James L. Lowry, MD
Private Practice-Radiology, Albuquerque

Alice M. Luna, MD
Private Practice-Pediatrics, Albuquerque

Gregory Mertz, MD
Department of Medicine, Infectious Disease, University of New Mexico School of Medicine, Albuquerque

Darwin L. Palmer, MD
Chief, Division of Infectious Disease, Veterans Administration Medical Center; Chief, Division of Infectious Disease, Department of Medicine, University of New Mexico School of Medicine, Albuquerque

Donald Romig, MD
Private Practice, Internal Medicine, Infectious Disease, Santa Fe, New Mexico

Toby Simon, MD
Medical Director, United Blood Services, Albuquerque

Charles Thompson, MD
Radiologist, Emeritus, Albuquerque

William Thompson, MD
Chief, Radiology, Veterans Administration Medical Center, Chapel Hill, North Carolina

James Waltner, MD
Private Practice-Pediatrics, Espanola, New Mexico

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CARDIZEM® (diltiazem HCl) produces an incidence of adverse reactions not greater than that reported with placebo therapy, thus contributing to the patient's sense of well-being.

Reduces angina attack frequency*
42% to 46% decrease reported in multicenter study.[1]

Increases exercise tolerance*
In Bruce exercise test,[2] control patients averaged 8.0 minutes to onset of pain; Cardizem patients averaged 9.8 minutes ($P<.005$).

*Cardizem is indicated in the treatment of angina pectoris due to coronary artery spasm and in the management of chronic stable angina (classic effort-associated angina) in patients who cannot tolerate therapy with beta-blockers and/or nitrates or who remain symptomatic despite adequate doses of these agents.

References:

1. Strauss WE, McIntyre KM, Parisi AF, et al: Safety and efficacy of diltiazem hydrochloride for the treatment of stable angina pectoris: Report of a cooperative clinical trial. Am J Cardiol 49:560-566, 1982.
2. Pool PE, Seagren SC, Bonanno JA, et al: The treatment of exercise-inducible chronic stable angina with diltiazem: Effect on treadmill exercise. Chest 78 (July suppl):234-238, 1980.

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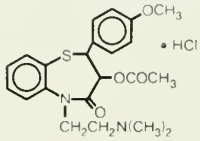
30 mg and 60 mg tablets

DESCRIPTION

CARDIZEM® (diltiazem hydrochloride) is a calcium ion influx inhibitor (slow channel blocker or calcium antagonist). Chemically, diltiazem hydrochloride is 1,5-Benzothiazepin-4(5H)one,3-(acetyloxy) -5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-, monohydrochloride,(+) -cis- The chemical structure is:



Diltiazem hydrochloride is a white to off-white crystalline powder with a bitter taste. It is soluble in water, methanol, and chloroform. It has a molecular weight of 450.98. Each tablet of CARDIZEM contains either 30 mg or 60 mg diltiazem hydrochloride for oral administration.

CLINICAL PHARMACOLOGY

The therapeutic benefits achieved with CARDIZEM are believed to be related to its ability to inhibit the influx of calcium ions during membrane depolarization of cardiac and vascular smooth muscle.

Mechanisms of Action. Although precise mechanisms of its antianginal actions are still being delineated, CARDIZEM is believed to act in the following ways:

1. Angina Due to Coronary Artery Spasm: CARDIZEM has been shown to be a potent dilator of coronary arteries both epicardial and subendocardial. Spontaneous and ergonovine-induced coronary artery spasm are inhibited by CARDIZEM.
2. Exertional Angina: CARDIZEM has been shown to produce increases in exercise tolerance, probably due to its ability to reduce myocardial oxygen demand. This is accomplished via reductions in heart rate and systemic blood pressure at submaximal and maximal exercise work loads.

In animal models, diltiazem interferes with the slow inward (depolarizing) current in excitable tissue. It causes excitation-contraction uncoupling in various myocardial tissues without changes in the configuration of the action potential. Diltiazem produces relaxation of coronary vascular smooth muscle and dilation of both large and small coronary arteries at drug levels which cause little or no negative inotropic effect. The resultant increases in coronary blood flow (epicardial and subendocardial) occur in ischemic and nonischemic models and are accompanied by dose-dependent decreases in systemic blood pressure and decreases in peripheral resistance.

Hemodynamic and Electrophysiologic Effects. Like other calcium antagonists, diltiazem decreases sinoatrial and atrioventricular conduction in isolated tissues and has a negative inotropic effect in isolated preparations. In the intact animal, prolongation of the AH interval can be seen at higher doses.

In man, diltiazem prevents spontaneous and ergonovine-provoked coronary artery spasm. It causes a decrease in peripheral vascular resistance and a modest fall in blood pressure and, in exercise tolerance studies in patients with ischemic heart disease, reduces the heart rate-blood pressure product for any given work load. Studies to date, primarily in patients with good ventricular function, have not revealed evidence of a negative inotropic effect; cardiac output, ejection fraction, and left ventricular end diastolic pressure have not been affected. There are as yet few data on the interaction of diltiazem and beta-blockers. Resting heart rate is usually unchanged or slightly reduced by diltiazem.

Intravenous diltiazem in doses of 20 mg prolongs AH conduction time and AV node functional and effective refractory periods approximately 20%. In a study involving single oral doses of 300 mg of CARDIZEM in six normal volunteers, the average maximum PR prolongation was 14% with no instances of greater than first-degree AV block. Diltiazem-associated prolongation of the AH interval is not more pronounced in patients with first-degree heart block. In patients with sick sinus syndrome, diltiazem significantly prolongs sinus cycle length (up to 50% in some cases).

Chronic oral administration of CARDIZEM in doses of up to 240 mg/day has resulted in small increases in PR interval, but has not usually produced abnormal prolongation. There were, however, three instances of second-degree AV block and one instance of third-degree AV block in a group of 959 chronically treated patients.

Pharmacokinetics and Metabolism. Diltiazem is absorbed from the tablet formulation to about 80% of a reference capsule and is subject to an extensive first-pass effect, giving an absolute bioavailability (compared to intravenous dosing) of about 40%. CARDIZEM undergoes extensive hepatic metabolism in which 2% to 4% of the unchanged drug appears in the urine. In vitro binding studies show CARDIZEM is 70% to 80% bound to plasma proteins. Competitive ligand binding studies have also shown CARDIZEM binding is not altered by therapeutic concentrations of digoxin, hydrochlorothiazide, phenylbutazone, propranolol, salicylic acid, or warfarin. Single oral doses of 30 to 120 mg of CARDIZEM result in detectable plasma levels within 30 to 60 minutes and peak plasma levels two to three hours after drug administration. The plasma elimination half-life following single or multiple drug administration is approximately 3.5 hours. Desacetyl diltiazem is also present in the plasma at levels of 10% to 20% of the parent drug and is 25% to 50% as potent a coronary vasodilator as diltiazem. Therapeutic blood levels of CARDIZEM appear to be in the range of 50 to 200 ng/ml. There is a departure from dose-linearity when single doses above 60 mg are given; a 120-mg dose gave blood levels three times that of the 60-mg dose. There is no information about the effect of renal or hepatic impairment on excretion or metabolism of diltiazem.

INDICATIONS AND USAGE

1. **Angina Pectoris Due to Coronary Artery Spasm.** CARDIZEM is indicated in the treatment of angina pectoris due to coronary artery spasm. CARDIZEM has been shown effective in the treatment of spontaneous coronary artery spasm presenting as Prinzmetal's variant angina (resting angina with ST-segment elevation occurring during attacks).
2. **Chronic Stable Angina (Classic Effort-Associated Angina).** CARDIZEM is indicated in the management of chronic stable angina. CARDIZEM has been effective in controlled trials in reducing angina frequency and increasing exercise tolerance.

There are no controlled studies of the effectiveness of the concomitant use of diltiazem and beta-blockers or of the safety of this combination in patients with impaired ventricular function or conduction abnormalities.

CONTRAINDICATIONS

CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker, and (3) patients with hypotension (less than 90 mm Hg systolic).

WARNINGS

1. **Cardiac Conduction.** CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (six of 1243 patients for 0.48%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.
2. **Congestive Heart Failure.** Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). Experience with the use of CARDIZEM alone or in combination with beta-blockers in patients with impaired ventricular function is very limited. Caution should be exercised when using the drug in such patients.
3. **Hypotension.** Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.
4. **Acute Hepatic Injury.** In rare instances, patients receiving CARDIZEM have exhibited reversible acute hepatic injury as evidenced by moderate to extreme elevations of liver enzymes. (See PRECAUTIONS and ADVERSE REACTIONS.)

PRECAUTIONS

General. CARDIZEM (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any new drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Drug Interaction. Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS).

Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers or digitalis is usually well tolerated. Available data are not sufficient, however, to predict the effects of concomitant treatment, particularly in patients with left ventricular dysfunction or cardiac conduction abnormalities. In healthy volunteers, diltiazem has been shown to increase serum digoxin levels up to 20%.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response in in vitro bacterial tests. No intrinsic effect on fertility was observed in rats.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

There are no well-controlled studies in pregnant women; therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when CARDIZEM is administered to a nursing woman if the drug's benefits are thought to outweigh its potential risks in this situation.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded.

In domestic placebo-controlled trials, the incidence of adverse reactions reported during CARDIZEM therapy was not greater than that reported during placebo therapy.

The following represent occurrences observed in clinical studies which can be at least reasonably associated with the pharmacology of calcium influx inhibition. In many cases, the relationship to CARDIZEM has not been established. The most common occurrences, as well as their frequency of presentation, are: edema (2.4%), headache (2.1%), nausea (1.9%), dizziness (1.5%), rash (1.3%), asthenia (1.2%), AV block (1.1%). In addition, the following events were reported infrequently (less than 1%) with the order of presentation corresponding to the relative frequency of occurrence.

Cardiovascular:	Flushing, arrhythmia, hypotension, bradycardia, palpitations, congestive heart failure, syncope.
Nervous System:	Paresthesia, nervousness, somnolence, tremor, insomnia, hallucinations, and amnesia.
Gastrointestinal:	Constipation, dyspepsia, diarrhea, vomiting, mild elevations of alkaline phosphatase, SGOT, SGPT, and LDH.
Dermatologic:	Pruritus, petechiae, urticaria, photosensitivity.
Other.	Polyuria, nocturia.

The following additional experiences have been noted.

A patient with Prinzmetal's angina experiencing episodes of vasospastic angina developed periods of transient asymptomatic asystole approximately five hours after receiving a single 60-mg dose of CARDIZEM.

The following postmarketing events have been reported infrequently in patients receiving CARDIZEM: erythema multiforme; leukopenia; and extreme elevations of alkaline phosphatase, SGOT, SGPT, LDH, and CPK. However, a definitive cause and effect between these events and CARDIZEM therapy is yet to be established.

OVERDOSAGE OR EXAGGERATED RESPONSE

Overdosage experience with oral diltiazem has been limited. Single oral doses of 300 mg of CARDIZEM have been well tolerated by healthy volunteers. In the event of overdosage or exaggerated response, appropriate supportive measures should be employed in addition to gastric lavage. The following measures may be considered:

Bradycardia	Administer atropine (0.60 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.
High-Degree AV Block	Treat as for bradycardia above. Fixed high-degree AV block should be treated with cardiac pacing.
Cardiac Failure	Administer inotropic agents (isoproterenol, dopamine, or dobutamine) and diuretics.
Hypotension	Vasopressors (eg, dopamine or levarterenol bitartrate).

Actual treatment and dosage should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

The oral/LD_{50}'s in mice and rats range from 415 to 740 mg/kg and from 560 to 810 mg/kg, respectively. The intravenous LD_{50}'s in these species were 60 and 38 mg/kg, respectively. The oral LD_{50} in dogs is considered to be in excess of 50 mg/kg, while lethality was seen in monkeys at 360 mg/kg. The toxic dose in man is not known, but blood levels in excess of 800 ng/ml have not been associated with toxicity.

DOSAGE AND ADMINISTRATION

Exertional Angina Pectoris Due to Atherosclerotic Coronary Artery Disease or Angina Pectoris at Rest Due to Coronary Artery Spasm. Dosage must be adjusted to each patient's needs. Starting with 30 mg four times daily, before meals and at bedtime, dosage should be increased gradually (given in divided doses three or four times daily) at one- to two-day intervals until optimum response is obtained. Although individual patients may respond to any dosage level, the average optimum dosage range appears to be 180 to 240 mg/day. There are no available data concerning dosage requirements in patients with impaired renal or hepatic function. If the drug must be used in such patients, titration should be carried out with particular caution.

Concomitant Use With Other Antianginal Agents:

1. **Sublingual NTG** may be taken as required to abort acute anginal attacks during CARDIZEM therapy.
2. **Prophylactic Nitrate Therapy**—CARDIZEM may be safely coadministered with short- and long-acting nitrates, but there have been no controlled studies to evaluate the antianginal effectiveness of this combination.
3. **Beta-blockers.** (See WARNINGS and PRECAUTIONS.)

HOW SUPPLIED

Cardizem 30-mg tablets are supplied in bottles of 100 (NDC 0088-1771-47) and in Unit Dose Identification Paks of 100 (NDC 0088-1771-49). Each green tablet is engraved with MARION on one side and 1771 engraved on the other. CARDIZEM 60-mg scored tablets are supplied in bottles of 100 (NDC 0088-1772-47) and in Unit Dose Identification Paks of 100 (NDC 0088-1772-49). Each yellow tablet is engraved with MARION on one side and 1772 on the other.

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Annual Scientific Session

July 25-26, 1985 • Sun Valley, Idaho

THURSDAY, JULY 25

8:00 a.m. **Update on Pathophysiology of Peptic Ulcer Disease**
Keith G. Tolman, MD, *Associate Professor of Medicine*
The University of Utah School of Medicine
Salt Lake City

9:00 a.m. **Dysphagia: A Common Clinical Problem**
Jorge E. Valenzuela, MD, *Professor of Medicine*
University of Southern California School of Medicine
Los Angeles

10:30 a.m. **Evaluation and Surgical Management**
Thomas R. DeMeester, MD, *Professor and Chairman, Department of Surgery*
Creighton University School of Medicine
Omaha

11:30 a.m. **Disorders of Gastric Emptying**
Jorge E. Valenzuela, MD

2:00 p.m. **Implications of Hepatitis B in Health Care Workers**
Keith G. Tolman, MD

3:00 p.m. **Preoperative Evaluation of Patients with Gastroesophageal Reflux**
Thomas R. DeMeester, MD

4:00 p.m. **Panel Discussion**

FRIDAY, JULY 26

8:00 a.m. **Implications of DRG's in Care of the Cancer Patient**
Albert M. Brady, MD
Medical Oncologist in Private Practice
Portland

9:00 a.m. **Thyroid Nodules: A Practical Approach to Management**
Kenneth E. W. Melvin, MD, *Chief of Medicine and Brill Professor*
St Vincent's Hospital
Portland

10:30 a.m. **Pain Control: With Emphasis on Terminal Disease**
Albert M. Brady, MD

11:30 a.m. **Estrogens and Osteoporosis**
Kenneth E. W. Melvin, MD

12:30 p.m. **Adjourn**

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BE/BC INTERNIST needed to associate with busy Internist in Wyoming. Growing community, excellent schools, new hospital, and great skiing and recreational opportunities nearby. Available now or summer, 1985. Send CV to Box 6461, Western Journal of Medicine, 44 Gough St., San Francisco, CA 94103.

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FAMILY PHYSICIAN AND OB/GYN CONSULTANT for growing Primary Care Health Center in South Bay Area. Must be Board certified or eligible. Spanish speaking preferred. Send CV to Gardner Community Health Center, 325 Willow Street, San Jose, CA 95110 or call Norma at (408) 998-2264. EOE M/F/H.

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(Continued on Page 592)

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(Continued from Page 590)

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INTERNIST WANTED to associate with Allergist/Rheumatologist with established practice in San Diego, California. Send Vitae to W. B. Pincus, MD, 2602 First Ave., San Diego, CA 92103.

PHYSICIANS WANTED

ACADEMIC NEUROLOGISTS, General Internists, Cardiologist—wanted for full-time faculty positions. Must be Board admissible or certified, interested in teaching medical students and house staff. Good balance between clinical practice and teaching with research opportunities available. Assistant Professor level with excellent guaranteed salary and benefits. Send CV to Victor H. Kaylarian, DO, Department of Medicine, University of Osteopathic Medicine and Health Sciences, 3200 Grand Avenue, Des Moines, IA 50312. All inquiries confidential.

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(Continued on Page 594)

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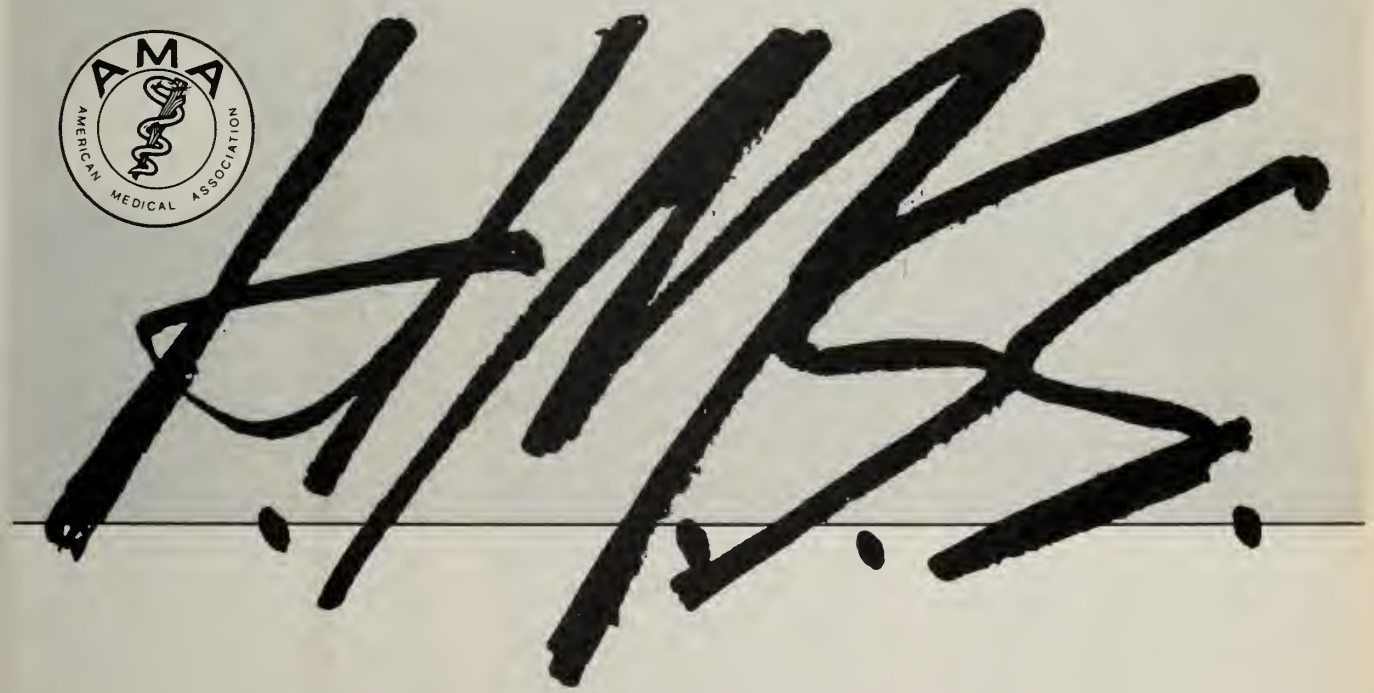

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CLINICAS DEL CAMINO REAL, INC. is seeking two Family Practice Physicians to augment its medical practice. Pay range is $4,200 to $4,800 per month, plus share of inpatient work. Fringe benefits include: three weeks vacation, sick leave, tax deferred annuity plan, twelve holidays and an excellent working environment located in Ventura County. Send résumé to: Robert S. Juarez, Executive Director, PO Box 4878, Ventura, CA 93004. Knowledge of Spanish desirable. An EOE.

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PHYSICIANS WANTED—Opportunities available in OB/GYN, Ophthalmology, and Orthopaedics in Northern California. Send CV to Box 6469, Western Journal of Medicine, 44 Gough St., San Francisco, CA 94103.

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Alaska State Medical Association—4107 Laurel St., Anchorage 99504. (907) 562-2662. Annual Meeting: June 5-8, 1985, Haines.

Arizona Medical Association, Inc.—810 W. Bethany Home Rd., Phoenix 85013. (602) 246-8901. Annual Meeting: April 26-27, 1985, The Cottonwoods, Scottsdale.

California Medical Association—44 Gough St., San Francisco 94103. (415) 863-5522. Annual Meeting: February 28-March 5, 1986, Bonaventure Hotel, Los Angeles.

Colorado Medical Society—6825 E. Tennessee, Bldg. 2, Suite 500, Denver 80224. (303) 321-8590. Annual Meeting: September 11-14, 1985, Broadmoor, Colorado Springs.

Hawaii Medical Association—320 Ward Ave., Suite 200, Honolulu 96814. (808) 536-7702. Annual Meeting: October 12-14, 1985, Kona Surf Hotel, Kona.

Idaho Medical Association—305 W. Jefferson, PO Box 2668, Boise 83701. (208) 344-7888. Annual Meeting: July 24-27, 1985, Sun Valley.

Montana Medical Association—2012 11th Ave., Suite 12, Helena 59601. (406) 443-4000. Annual Meeting: October 3-5, 1985, Outlaw Inn, Kalispell.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: May 9-12, 1985, Hyatt, Lake Tahoe.

New Mexico Medical Society—303 San Mateo NE, Suite 204, Albuquerque 87108. (505) 266-7868. Annual Meeting: May 1-3, 1985, Marriott, Albuquerque.

Oregon Medical Association—5210 S.W. Corbett Ave., Portland 97201. (503) 226-1555. Annual Meeting: (House of Delegates only): April 26-28, 1985, Ashland Hills Inn, Ashland.

Utah State Medical Association—540 East Fifth South, Salt Lake City 84102. (801) 355-7477. Annual Meeting: September 26-27, 1985. Hotel Utah, Salt Lake City.

Washington State Medical Association—900 United Airlines Bldg., 2033 6th Ave., Seattle 98121. (206) 623-4801. Annual Meeting: September 19-22, 1985, Jantzen Beach.

Wyoming Medical Society—P.O. Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. Annual Meeting: June 23-26, 1985, Jackson Lake Lodge, Moran.

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***Usage in Pregnancy*: Use of minor tranquilizers during the first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Since physical and psychological dependence to chlordiazepoxide have been reported rarely, use caution in administering Limbitrol to addiction-prone individuals or those who might increase dosage; withdrawal symptoms following discontinuation of either component alone have been reported (nausea, headache and malaise for amitriptyline; symptoms [including convulsions] similar to those of barbiturate withdrawal for chlordiazepoxide).

Precautions: Use with caution in patients with a history of seizures, in hyperthyroid patients or those on thyroid medication, and in patients with impaired renal or hepatic function. Because of the possibility of suicide in depressed patients, do not permit easy access to large quantities in these patients. Periodic liver function tests and blood counts are recommended during prolonged treatment. Amitriptyline component may block action of guanethidine or similar antihypertensives. Concomitant use with other psychotropic drugs has not been evaluated, sedative effects may be additive. Discontinue several days before surgery. Limit concomitant administration of ECT to essential treatment. See Warnings for precautions about pregnancy. Limbitrol should not be taken during the nursing period. Not recommended in children under 12. In the elderly and debilitated, limit to smallest effective dosage to preclude ataxia, oversedation, confusion or anticholinergic effects.

Adverse Reactions: Most frequently reported are those associated with either component alone: drowsiness, dry mouth, constipation, blurred vision, dizziness and bloating. Less frequently occurring reactions include vivid dreams, impotence, tremor, confusion and nasal congestion. Many depressive symptoms including anorexia, fatigue, weakness, restlessness and lethargy have been reported as side effects of both Limbitrol and amitriptyline. Granulocytopenia, jaundice and hepatic dysfunction have been observed rarely.

The following list includes adverse reactions not reported with Limbitrol but requiring consideration because they have been reported with one or both components or closely related drugs:

Cardiovascular: Hypotension, hypertension, tachycardia, palpitations, myocardial infarction, arrhythmias, heart block, stroke.

Psychiatric: Euphoria, apprehension, poor concentration, delusions, hallucinations, hypomania and increased or decreased libido.

Neurologic: Incoordination, ataxia, numbness, tingling and paresthesias of the extremities, extrapyramidal symptoms, syncope, changes in EEG patterns.

Anticholinergic: Disturbance of accommodation, paralytic ileus, urinary retention, dilatation of urinary tract.

Allergic: Skin rash, urticaria, photosensitization, edema of face and tongue, pruritus.

Hematologic: Bone marrow depression including agranulocytosis, eosinophilia, purpura, thrombocytopenia.

Gastrointestinal: Nausea, epigastric distress, vomiting, anorexia, stomatitis, peculiar taste, diarrhea, black tongue.

Endocrine: Testicular swelling and gynecomastia in the male, breast enlargement, galactorrhea and minor menstrual irregularities in the female, elevation and lowering of blood sugar levels, and syndrome of inappropriate ADH (antidiuretic hormone) secretion.

Other: Headache, weight gain or loss, increased perspiration, urinary frequency, mydriasis, jaundice, alopecia, parotid swelling.

Overdosage: Immediately hospitalize patient suspected of having taken an overdose. Treatment is symptomatic and supportive. I.V. administration of 1 to 3 mg physostigmine salicylate has been reported to reverse the symptoms of amitriptyline poisoning. See complete product information for manifestation and treatment.

Dosage: Individualize according to symptom severity and patient response. Reduce to smallest effective dosage when satisfactory response is obtained. Larger portion of daily dose may be taken at bedtime. Single *h.s.* dose may suffice for some patients. Lower dosages are recommended for the elderly.

Limbitrol DS (double strength) Tablets, initial dosage of three or four tablets daily in divided doses, increased to six tablets or decreased to two tablets daily as required. Limbitrol Tablets, initial dosage of three or four tablets daily in divided doses, for patients who do not tolerate higher doses.

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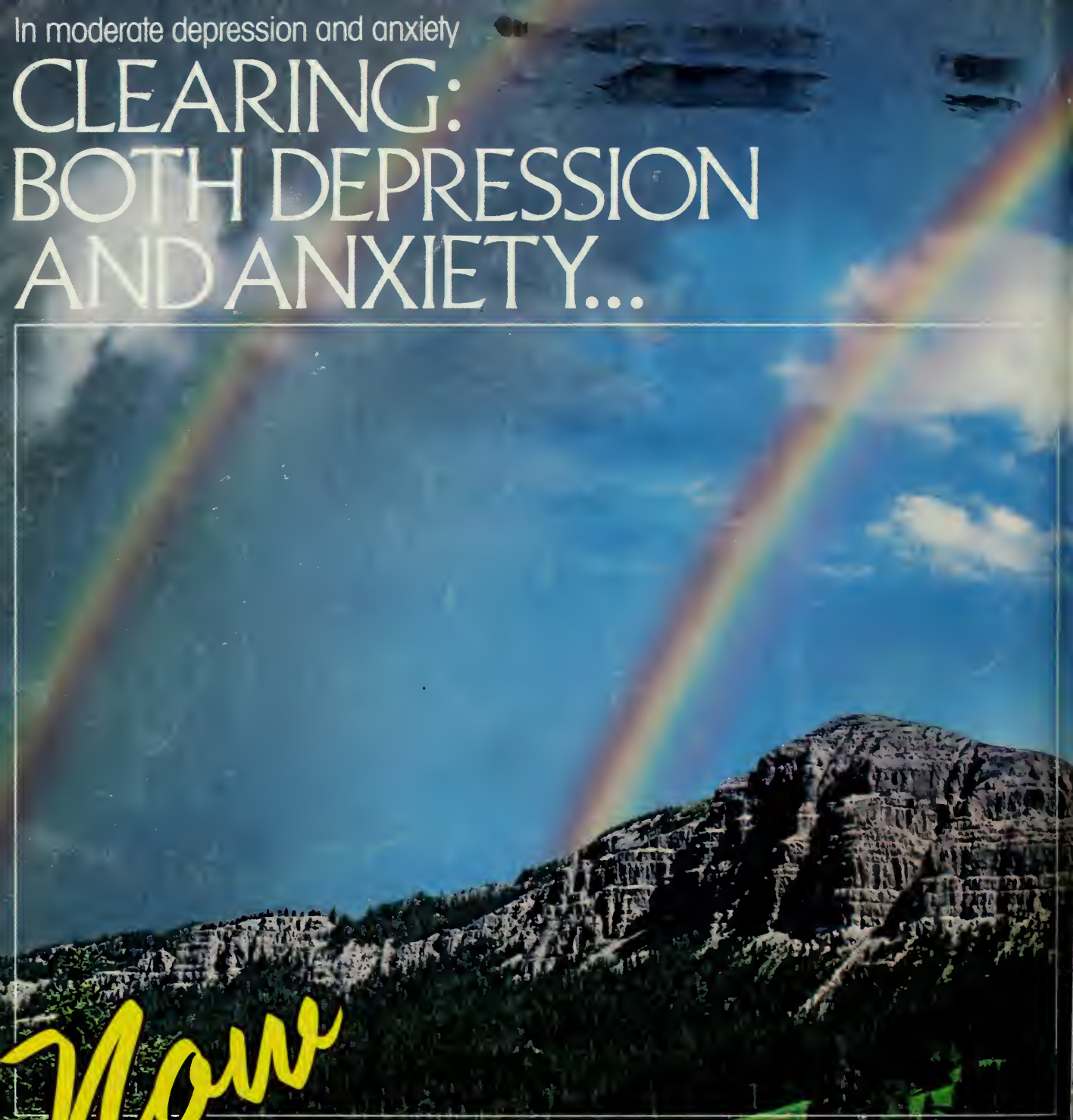

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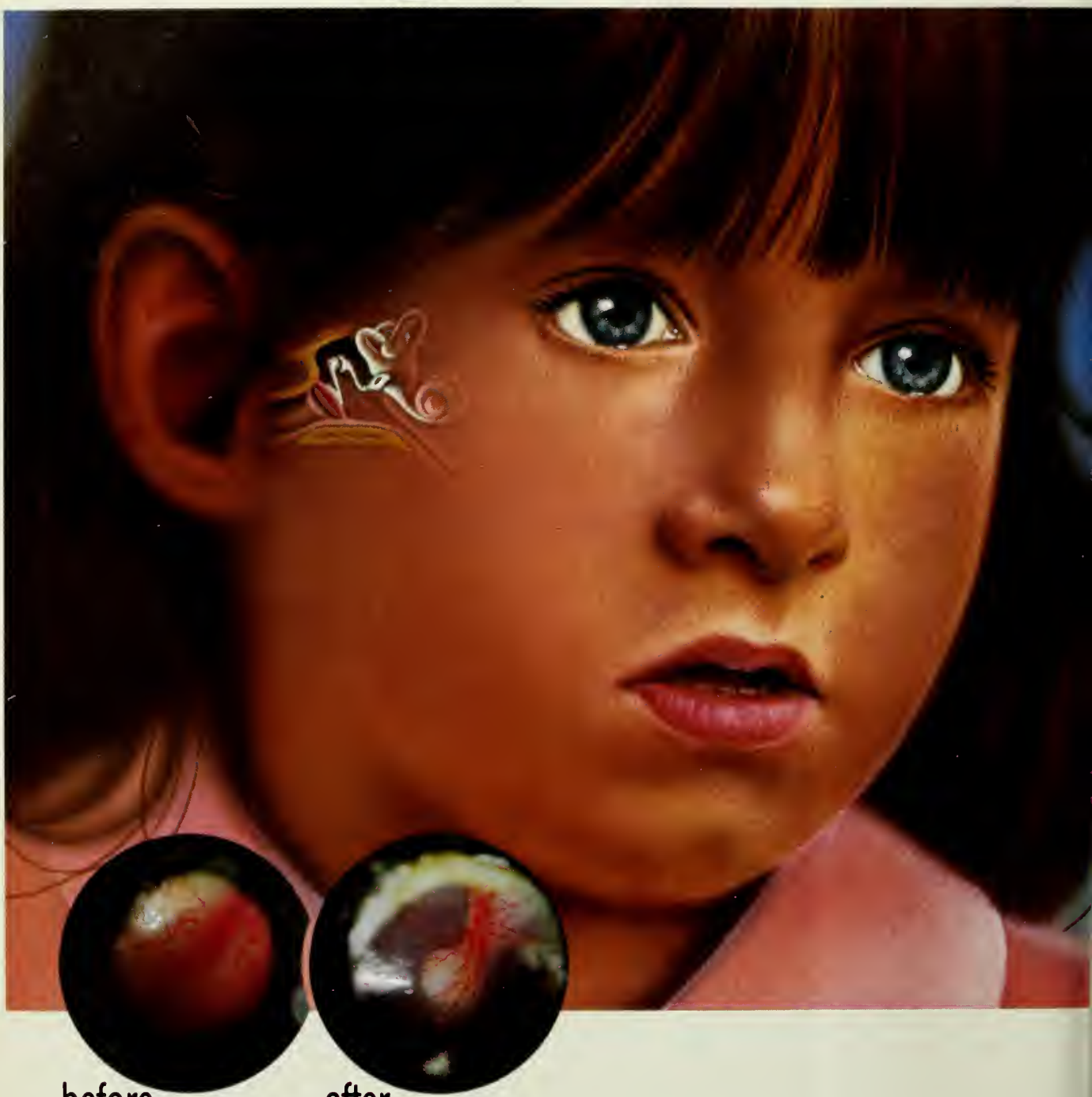

before Otoscopic view of tympanic membrane in a patient who did not respond to ampicillin

after Same patient after ten days of Bactrim (trimethoprim and sulfamethoxazole/Roche) therapy

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References: 1. Klimek JJ *et al: J Pediatr 96:*1087-1089, Jun 1980. 2. Schwartz RH *et al: Rev Infect Dis 4:*514-516, Mar-Apr 1982. 3. Cooper J, Inman JS, Dawson AF: *Practitioner 217:*804-809, Nov 1976. 4. Antibiotic Sensitivity Report, Winter 1983. BAC-DATA Medical Information Systems, Inc. 5. Data on file, Hoffmann-La Roche Inc., Nutley, NJ. 6. Wormser GP, Keusch GT, Heel RC: *Drugs 24:*459-518, Dec 1982. 7. *Med Lett Drugs Ther 23:*93-95, Oct 30, 1981.

Please see summary of product information on the following page.

References: 1. Klimek JJ *et al: J Pediatr* 96:1087-1089, Jun 1980. 2. Schwartz RH *et al: Rev Infect Dis* 4:514-516, Mar-Apr 1982. 3. Cooper J, Inman JS, Dawson AF: *Practitioner* 217:804-809, Nov 1976. 4. Antibiotic Sensitivity Report, Winter 1983. BAC-DATA Medical Information Systems, Inc. 5. Data on file, Hoffmann-La Roche Inc., Nutley, NJ. 6. Wormser GP, Keusch GT, Heel RC: *Drugs* 24:459-518, Dec 1982. 7. *Med Lett Drugs Ther* 23:93-95, Oct 30, 1981.

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Before prescribing, please consult complete product information, a summary of which follows:

Indications and Usage: For the treatment of urinary tract infections due to susceptible strains of the following organisms: *Escherichia coli, Klebsiella-Enterobacter, Proteus mirabilis, Proteus vulgaris, Proteus morganii*. It is recommended that initial episodes of uncomplicated urinary tract infections be treated with a single effective antibacterial agent rather than the combination. *Note:* The increasing frequency of resistant organisms limits the usefulness of all antibacterials, especially in these urinary tract infections.

For acute otitis media in children due to susceptible strains of *Haemophilus influenzae* or *Streptococcus pneumoniae* when in physician's judgment it offers an advantage over other antimicrobials. To date, there are limited data on the safety of repeated use of Bactrim in children under two years of age. Bactrim is not indicated for prophylactic or prolonged administration in otitis media at any age.

For acute exacerbations of chronic bronchitis in adults due to susceptible strains of *Haemophilus influenzae* or *Streptococcus pneumoniae* when in physician's judgment it offers an advantage over a single antimicrobial agent.

For enteritis due to susceptible strains of *Shigella flexneri* and *Shigella sonnei* when antibacterial therapy is indicated.

Also for the treatment of documented *Pneumocystis carinii* pneumonitis.

Contraindications: Hypersensitivity to trimethoprim or sulfonamides; patients with documented megaloblastic anemia due to folate deficiency; pregnancy at term; nursing mothers because sulfonamides are excreted in human milk and may cause kernicterus; infants less than 2 months of age.

Warnings: BACTRIM SHOULD NOT BE USED TO TREAT STREPTOCOCCAL PHARYNGITIS. Clinical studies show that patients with group A β-hemolytic streptococcal tonsillopharyngitis have higher incidence of bacteriologic failure when treated with Bactrim than do those treated with penicillin. Deaths from hypersensitivity reactions, hepatocellular necrosis, agranulocytosis, aplastic anemia and other blood dyscrasias have been associated with sulfonamides. Experience with trimethoprim is much more limited but occasional interference with hematopoiesis has been reported as well as an increased incidence of thrombopenia with purpura in elderly patients on certain diuretics, primarily thiazides. Sore throat, fever, pallor, purpura or jaundice may be early signs of serious blood disorders. Frequent CBC's are recommended; therapy should be discontinued if a significantly reduced count of any formed blood element is noted.

Precautions: *General:* Use cautiously in patients with impaired renal or hepatic function, possible folate deficiency, severe allergy or bronchial asthma. In patients with glucose-6-phosphate dehydrogenase deficiency, hemolysis, frequently dose-related, may occur. During therapy, maintain adequate fluid intake and perform frequent urinalyses, with careful microscopic examination, and renal function tests, particularly where there is impaired renal function. Bactrim may prolong prothrombin time in those receiving warfarin; reassess coagulation time when administering Bactrim to these patients.

Pregnancy: Teratogenic Effects: Pregnancy Category C. Because trimethoprim and sulfamethoxazole may interfere with folic acid metabolism, use during pregnancy only if potential benefits justify the potential risk to the fetus.

Adverse Reactions: All major reactions to sulfonamides and trimethoprim are included, even if not reported with Bactrim. *Blood dyscrasias:* Agranulocytosis, aplastic anemia, megaloblastic anemia, thrombopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia and methemoglobinemia. *Allergic reactions:* Erythema multiforme, Stevens-Johnson syndrome, generalized skin eruptions, epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia and allergic myocarditis. *Gastrointestinal reactions:* Glossitis, stomatitis, nausea, emesis, abdominal pains, hepatitis, hepatocellular necrosis, diarrhea, pseudomembranous colitis and pancreatitis. *CNS reactions:* Headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo, insomnia, apathy, fatigue, muscle weakness and nervousness. *Miscellaneous reactions:* Drug fever, chills, toxic nephrosis with oliguria and anuria, periarteritis nodosa and L.E. phenomenon. Due to certain chemical similarities to some goitrogens, diuretics (acetazolamide, thiazides) and oral hypoglycemic agents, sulfonamides have caused rare instances of goiter production, diuresis and hypoglycemia in patients; cross-sensitivity with these agents may exist. In rats, long-term therapy with sulfonamides has produced thyroid malignancies.

Dosage: Not recommended for infants less than two months of age.

URINARY TRACT INFECTIONS AND SHIGELLOSIS IN ADULTS AND CHILDREN, AND ACUTE OTITIS MEDIA IN CHILDREN:

Adults: Usual adult dosage for urinary tract infections—1 DS tablet (double strength), 2 tablets (single strength) or 4 teasp. (20 ml) b.i.d. for 10-14 days. Use identical daily dosage for 5 days for shigellosis.

Children: Recommended dosage for children with urinary tract infections or acute otitis media—8 mg/kg trimethoprim and 40 mg/kg sulfamethoxazole per 24 hours, in two divided doses for 10 days. Use identical daily dosage for 5 days for shigellosis.

For patients with renal impairment: Use recommended dosage regimen when creatinine clearance is above 30 ml/min. If creatinine clearance is between 15 and 30 ml/min, use one-half the usual regimen. Bactrim is not recommended if creatinine clearance is below 15 ml/min.

ACUTE EXACERBATIONS OF CHRONIC BRONCHITIS IN ADULTS:

Usual adult dosage: 1 DS tablet (double strength), 2 tablets (single strength) or 4 teasp. (20 ml) b.i.d. for 14 days.

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Recommended dosage: 20 mg/kg trimethoprim and 100 mg/kg sulfamethoxazole per 24 hours in equal doses every 6 hours for 14 days. See complete product information for suggested children's dosage table.

Supplied: *Double Strength (DS) tablets*, each containing 160 mg trimethoprim and 800 mg sulfamethoxazole, bottles of 100, 250 and 500; Tel-E-Dose® packages of 100; Prescription Paks of 20. *Tablets*, each containing 80 mg trimethoprim and 400 mg sulfamethoxazole—bottles of 100 and 500; Tel-E-Dose® packages of 100; Prescription Paks of 40. *Pediatric Suspension*, containing 40 mg trimethoprim and 200 mg sulfamethoxazole per teaspoonful (5 ml); cherry flavored—bottles of 100 ml and 16 oz (1 pint). *Suspension*, containing 40 mg trimethoprim and 200 mg sulfamethoxazole per teaspoonful (5 ml); fruit-licorice flavored—bottles of 16 oz (1 pint).

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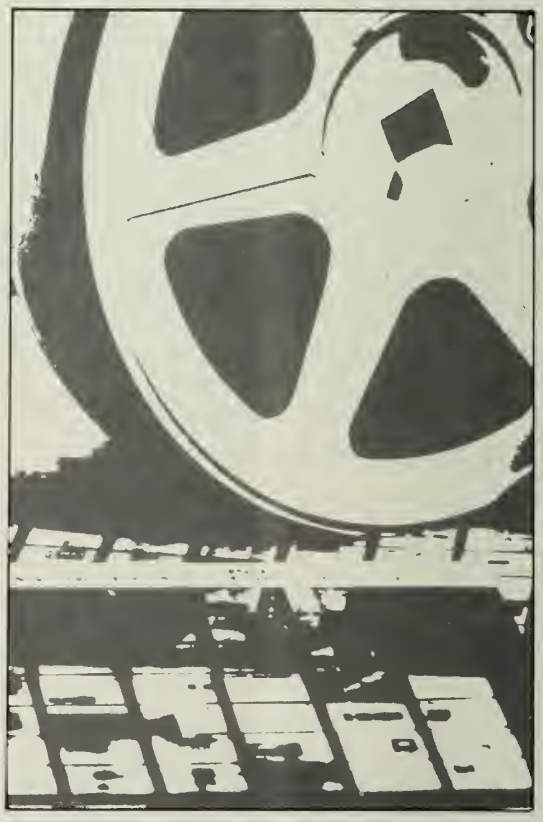

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Please consult full prescribing information before use. A summary follows:

INDICATIONS AND USAGE: SORBITRATE (isosorbide dinitrate) is indicated for the treatment and prevention of angina pectoris. All dosage forms of isosorbide dinitrate may be used prophylactically to decrease frequency and severity of anginal attacks and can be expected to decrease the need for sublingual nitroglycerin.

The sublingual and chewable forms of the drug are indicated for acute prophylaxis of angina pectoris when taken a few minutes before situations likely to provoke anginal attacks. Because of a slower onset of effect, the oral forms of isosorbide dinitrate are not indicated for acute prophylaxis.

CONTRAINDICATIONS: SORBITRATE is contraindicated in patients who have shown purported hypersensitivity or idiosyncrasy to it or other nitrates or nitrites. Epinephrine and related compounds are ineffective in reversing the severe hypotensive events associated with overdose and are contraindicated in this situation.

WARNINGS: The benefits of SORBITRATE during the early days of an acute myocardial infarction have not been established. If one elects to use organic nitrates in early infarction, hemodynamic monitoring and frequent clinical assessment should be used because of the potential deleterious effects of hypotension.

PRECAUTIONS: General: Severe hypotensive response, particularly with upright posture, may occur with even small doses of SORBITRATE. The drug should therefore be used with caution in subjects who may have blood volume depletion from diuretic therapy or in subjects who have low systolic blood pressure (eg, below 90 mmHg). Paradoxical bradycardia and increased angina pectoris may accompany nitrate-induced hypotension. Nitrate therapy may aggravate the angina caused by hypertrophic cardiomyopathy.

Marked symptomatic, orthostatic hypotension has been reported when calcium channel blockers and organic nitrates were used in combination. Dose adjustment of either class of agents may be necessary.

Tolerance to this drug and cross-tolerance to other nitrates and nitrites may occur. Tolerance to the vascular and antianginal effects of isosorbide dinitrate or nitroglycerin has been demonstrated in clinical trials, experience through occupational exposure, and in isolated tissue experiments in the laboratory. The importance of tolerance to the appropriate use of isosorbide dinitrate in the management of patients with angina pectoris has not been determined. However, one clinical trial using treadmill exercise tolerance (as an end point) found an 8-hour duration of action of oral isosorbide dinitrate following the first dose (after a 2-week placebo washout) and only a 2-hour duration of effect of the same dose after 1 week of repetitive dosing at conventional dosing intervals. On the other hand, several trials have been able to differentiate isosorbide dinitrate from placebo after 4 weeks of therapy and, in open trials, an effect seems detectable for as long as several months.

Tolerance clearly occurs in industrial workers continuously exposed to nitroglycerin. Moreover, physical dependence also occurs since chest pain, acute myocardial infarction, and even sudden death have occurred during temporary withdrawal of nitroglycerin from the workers. In clinical trials in angina patients, there are reports of anginal attacks being more easily provoked and of rebound in the hemodynamic effects soon after nitrate withdrawal. The relative importance of these observations to the routine, clinical use of isosorbide dinitrate is not known. However, it seems prudent to gradually withdraw patients from isosorbide dinitrate when the therapy is being terminated, rather than stopping the drug abruptly.

Information for Patients: Headache may occur during initial therapy with SORBITRATE. Headache is usually relieved by the use of standard headache remedies or by lowering the dose and tends to disappear after the first week or two of use.

Drug Interactions: Alcohol may enhance any marked sensitivity to the hypotensive effect of nitrates.

Isosorbide dinitrate acts directly on vascular smooth muscle; therefore, any other agent that depends on vascular smooth muscle as the final common path can be expected to have decreased or increased effect depending on the agent.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No long-term studies in animals have been performed to evaluate the carcinogenic potential of this drug. A modified two-litter reproduction study in rats fed isosorbide dinitrate at 25 or 100 mg/kg/day did not reveal any effects on fertility or gestation or any remarkable gross pathology in any parent or offspring fed isosorbide dinitrate as compared with rats fed a basal-controlled diet.

Pregnancy Category C: Isosorbide dinitrate has been shown to cause a dose-related increase in embryotoxicity (increase in mummified pups) in rabbits at oral doses 35 and 150 times the maximum recommended human daily dose. There are no adequate and well-controlled studies in pregnant women. SORBITRATE should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when SORBITRATE is administered to a nursing woman.

Pediatric Use: The safety and effectiveness of SORBITRATE in children has not been established.

ADVERSE REACTIONS: Adverse reactions, particularly headache and hypotension, are dose-related. In clinical trials at various doses, the following have been observed.

Headache is the most common (reported incidence varies widely, apparently being dose-related, with an average occurrence of about 25%) adverse reaction and may be severe and persistent. Cutaneous vasodilation with flushing may occur. Transient episodes of dizziness and weakness, as well as other signs of cerebral ischemia associated with postural hypotension, may occasionally develop (the incidence of reported symptomatic hypotension ranges from 2% to 36%). An occasional individual will exhibit marked sensitivity to the hypotensive effects of nitrates and severe responses (nausea, vomiting, weakness, restlessness, pallor, perspiration, and collapse) may occur even with the usual therapeutic dose. Drug rash and/or exfoliative dermatitis may occasionally occur. Nausea and vomiting appear to be uncommon. Case reports of clinically significant methemoglobinemia are rare at conventional doses of organic nitrates. The formation of methemoglobin is dose-related and, in the case of genetic abnormalities of hemoglobin that favor methemoglobin formation, even conventional doses of organic nitrate could produce harmful concentrations of methemoglobin.

DOSAGE AND ADMINISTRATION: For the treatment of angina pectoris, the usual starting dose for sublingual SORBITRATE is 2.5 to 5 mg; for chewable tablets, 5 mg; for oral (swallowed) tablets, 5 to 20 mg; and for controlled-release forms, 40 mg.

SORBITRATE should be titrated upward until angina is relieved or side effects limit the dose. In ambulatory patients, the magnitude of the incremental dose increase should be guided by measurements of standing blood pressure.

The initial dosage of sublingual or chewable SORBITRATE for prophylactic therapy in angina pectoris patients is generally 5 or 10 mg every 2 to 3 hours. Adequate controlled clinical studies demonstrating the effectiveness of chronic maintenance therapy with these dosage forms have not been reported.

SORBITRATE in oral doses of 10 to 40 mg given every 6 hours or in oral controlled-release doses of 40 to 80 mg given every 8 to 12 hours is generally recommended. The extent to which development of tolerance should modify the dosage program has not been defined. *The oral controlled-release forms of isosorbide dinitrate should not be chewed.*

DOSAGE FORMS AVAILABLE: Sublingual Tablets (2.5, 5, 10 mg), Chewable Tablets (5, 10 mg), Oral Tablets (5, 10, 20, 30, 40 mg); Sustained Action Tablets (40 mg).

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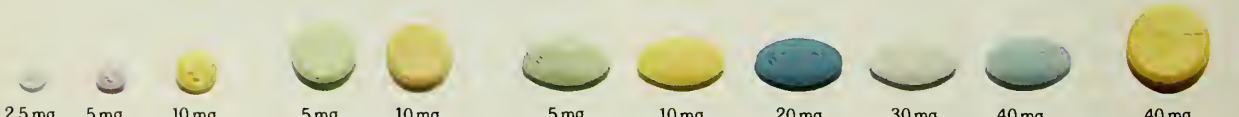

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Chief Discussant: RICHARD J. HABER, MD

A discussion selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco, School of Medicine. Taken from a transcription, it was prepared by Drs Homer A. Boushey, Associate Professor of Medicine, and David G. Warnock, Associate Professor of Medicine, under the direction of Dr Lloyd H. Smith, Jr, Professor of Medicine and Chair of the Department of Medicine.

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DESCRIPTION: Corgard (nadolol) is a synthetic nonselective beta-adrenergic receptor blocking agent.

CONTRAINDICATIONS: Bronchial asthma, sinus bradycardia and greater than first degree conduction block, cardiogenic shock, and overt cardiac failure (see WARNINGS).

WARNINGS: Cardiac Failure–Sympathetic stimulation may be a vital component supporting circulatory function in congestive heart failure, and its inhibition by beta-blockade may precipitate more severe failure. Although beta-blockers should be avoided in overt congestive heart failure, if necessary, they can be used with caution in patients with a history of failure who are well-compensated, usually with digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle. IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta-blockers can, in some cases, lead to cardiac failure; therefore, at first sign or symptom of heart failure, digitalize and/or give diuretics, and closely observe response, or discontinue nadolol (gradually if possible).

Exacerbation of Ischemic Heart Disease Following Abrupt Withdrawal– Hypersensitivity to catecholamines has been observed in patients withdrawn from beta-blocker therapy; exacerbation of angina and, in some cases, myocardial infarction have occurred after *abrupt* discontinuation of such therapy. When discontinuing chronic use of nadolol, particularly in patients with ischemic heart disease, gradually reduce dosage over a 1- to 2-week period and carefully monitor the patient. Reinstitute nadolol promptly (at least temporarily) and take other measures appropriate for management of unstable angina if angina markedly worsens or acute coronary insufficiency develops. Warn patients not to interrupt or discontinue therapy without physician's advice. Because coronary artery disease is common and may be unrecognized, it may be prudent not to discontinue nadolol therapy abruptly even in patients treated only for hypertension.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)– PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA-BLOCKERS. Administer nadolol with caution since it may block bronchodilation produced by endogenous or exogenous catecholamine stimulation of $beta_2$ receptors.

Major Surgery–Because beta blockade impairs the ability of the heart to respond to reflex stimuli and may increase risks of general anesthesia and surgical procedures, resulting in protracted hypotension or low cardiac output, it has generally been suggested that such therapy should be withdrawn several days prior to surgery. Recognition of the increased sensitivity to catecholamines of patients recently withdrawn from beta-blocker therapy, however, has made this recommendation controversial. If possible, withdraw beta-blockers well before surgery takes place. In emergency surgery, inform the anesthesiologist that the patient is on beta-blocker therapy. Use of beta-receptor agonists such as isoproterenol, dopamine, dobutamine, or levarterenol can reverse the effects of nadolol. Difficulty in restarting and maintaining the heart beat has also been reported with beta-adrenergic receptor blocking agents.

Diabetes and Hypoglycemia–Beta-adrenergic blockade may prevent the appearance of premonitory signs and symptoms (e.g., tachycardia and blood pressure changes) of acute hypoglycemia. This is especially important with labile diabetics. Beta-blockade also reduces release of insulin in response to hyperglycemia; therefore, it may be necessary to adjust dose of antidiabetic drugs.

Thyrotoxicosis–Beta-adrenergic blockade may mask certain clinical signs (e.g., tachycardia) of hyperthyroidism. To avoid abrupt withdrawal of beta-adrenergic blockade which might precipitate a thyroid storm, carefully manage patients suspected of developing thyrotoxicosis.

PRECAUTIONS: Impaired Hepatic or Renal Function–Use nadolol with caution in presence of either of these conditions (see DOSAGE AND ADMINISTRATION section of package insert).

Information for Patients–Warn patients, especially those with evidence of coronary artery insufficiency, against interruption or discontinuation of nadolol without physician's advice. Although cardiac failure rarely occurs in properly selected patients, advise patients being treated with beta-adrenergic blocking agents to consult physician at first sign or symptom of impending failure.

Drug Interactions–Catecholamine-depleting drugs (e.g., reserpine) may have an additive effect when given with beta-blocking agents. When treating patients with nadolol plus a catecholamine-depleting agent, carefully observe for evidence of hypotension and/or excessive bradycardia which may produce vertigo, syncope, or postural hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility–In 1 to 2 years' oral toxicologic studies in mice, rats, and dogs, nadolol did not produce significant toxic effects. In 2-year oral carcinogenic studies in rats and mice, nadolol did not produce neoplastic, preneoplastic, or nonneoplastic pathologic lesions.

Pregnancy–In animal reproduction studies with nadolol, evidence of embryo-and fetotoxicity was found in rabbits (but not in rats or hamsters) at doses 5 to 10 times greater (on a mg/kg basis) than maximum indicated human dose; no teratogenic potential was seen in any of these species. There are no well-controlled studies in pregnant women; therefore, use nadolol in pregnant women only if potential benefit justifies potential risk to the fetus.

Nursing Mothers–It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when nadolol is administered to a nursing woman. Animal studies showed that nadolol is found in the milk of lactating rats.

Pediatric Use–Safety and effectiveness in children have not been established.

ADVERSE REACTIONS: Most adverse effects have been mild and transient and have rarely required nadolol withdrawal.

Cardiovascular–Bradycardia with heart rates of less than 60 beats per minute occurs commonly, and heart rates below 40 beats per minute and/or symptomatic bradycardia were seen in about 2 of 100 patients. Symptoms of peripheral vascular insufficiency, usually of the Raynaud type, have occurred in approximately 2 of 100 patients. Cardiac failure, hypotension, and rhythm/conduction disturbances have each occurred in about 1 of 100 patients. Single instances of first degree and third degree heart block have been reported; intensification of AV block is a known effect of beta-blockers (see also CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS). **Central Nervous System**–Dizziness or fatigue reported in approximately 2 of 100 patients; paresthesias, sedation, and change in behavior reported in approximately 6 of 1000 patients. **Respiratory**–Bronchospasm reported in approximately 1 of 1000 patients (see CONTRAINDICATIONS and WARNINGS). **Gastrointestinal**– Nausea, diarrhea, abdominal discomfort, constipation, vomiting, indigestion, anorexia, bloating, and flatulence each reported in 1 to 5 of 1000 patients. **Miscellaneous**–Each of the following reported in 1 to 5 of 1000 patients: rash; pruritus; headache; dry mouth, eyes, or skin; impotence or decreased libido; facial swelling; weight gain; slurred speech; cough; nasal stuffiness; sweating; tinnitus; blurred vision. Although relationship to drug usage is not clear, sleep disturbances have been reported. The oculomucocutaneous syndrome associated with practolol has not been reported with nadolol.

Potential Adverse Effects: Although other adverse effects reported with other beta-adrenergic blocking agents have not been reported with nadolol, they should be considered potential adverse effects of nadolol. **Central Nervous System**–reversible mental depression progressing to catatonia; visual disturbances; hallucinations; an acute reversible syndrome characterized by disorientation for time and place; short-term memory loss, emotional lability with slightly clouded sensorium; decreased performance on neuropsychometrics. **Gastrointestinal**–mesenteric arterial thrombosis; ischemic colitis. **Hematologic**–agranulocytosis; thrombocytopenic or nonthrombocytopenic purpura. **Allergic**–fever combined with aching and sore throat; laryngospasm; respiratory distress. **Miscellaneous**–reversible alopecia; Peyronie's disease; erythematous rash.

OVERDOSAGE: Nadolol can be removed from the general circulation by hemodialysis. In addition to gastric lavage, employ the following measures as appropriate. In determining duration of corrective therapy, take note of long duration of effect of nadolol.

Excessive Bradycardia–Administer atropine (0.25 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.

Cardiac Failure–Administer a digitalis glycoside and diuretic. It has been reported that glucagon may also be useful in this situation.

Hypotension–Administer vasopressors, e.g., epinephrine or levarterenol. (There is evidence that epinephrine may be the drug of choice.)

Bronchospasm–Administer a $beta_2$-stimulating agent and/or a theophylline derivative.

DOSAGE: For all patients, DOSAGE MUST BE INDIVIDUALIZED.

For **angina pectoris,** usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 mg increments at 3 to 7 day intervals until optimum clinical response or pronounced slowing of the heart rate; usual maintenance dose is 80 to 240 mg q.d. (most patients respond to 160 mg or less daily). If treatment is to be discontinued, reduce dosage gradually over a period of 1 to 2 weeks (see WARNINGS).

For **hypertension,** usual initial dose is 40 mg q.d.; gradually increase in 40 to 80 mg increments until optimum blood pressure reduction is achieved; usual maintenance dose is 80 to 320 mg q.d. (rarely, doses up to 640 mg may be needed).

Patients with renal failure require adjustment in dosing interval; see package insert for dosage in these patients.

For full prescribing information, consult package insert.

HOW SUPPLIED: In scored tablets containing 40, 80, 120, or 160 mg nadolol per tablet in bottles of 100 and 1000 tablets and in Unimatic® unit-dose packs of 100 tablets.

SQUIBB

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The Joint National Committee now advocates beta-blockers for broad Step-1 usage

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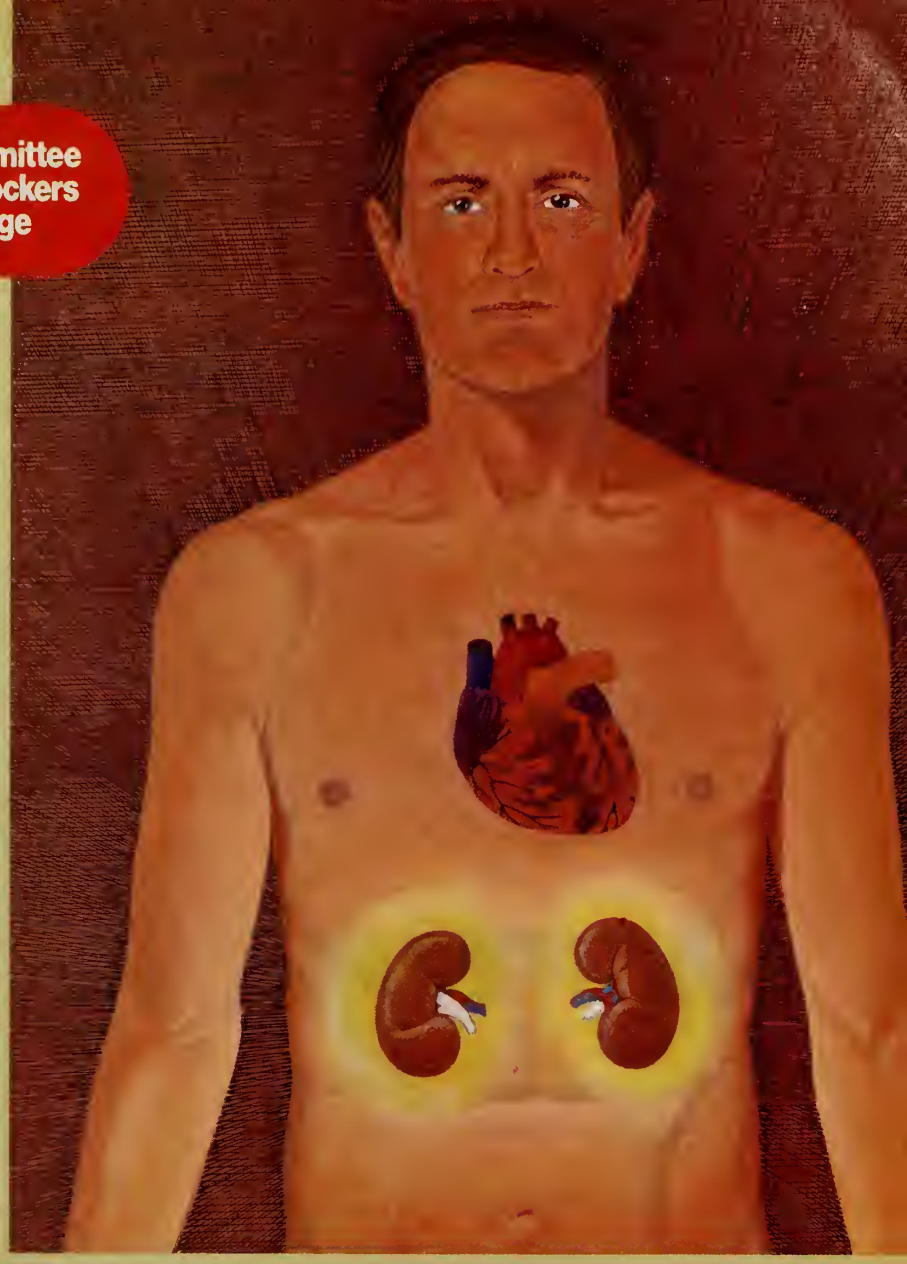

Effect on kidney

"...investigations suggest that the long-term use of nadolol, a long-acting nonselective agent, is associated with preserved renal function."[1]

"...the majority of investigators utilizing propranolol have reported decrements in RPF [renal plasma flow] and GFR [glomerular filtration rate]..."[1]

CORGARD® (nadolol tablets) should be used with caution in patients with impaired renal function.

Reference: 1. Epstein M, Oster JR: Beta-blockers and the kidney. Mineral Electrolyte Metab 8: 237-254, 1982.

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TAKE THE ADVANTAGE TO HEART

Please see the adjacent page of this advertisement for brief summary.

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The pain-relieving power of *Motrin* 600 mg tablets is welcome at any age. The advantages of *Motrin* become more important as patients grow older.

Advanced age has little or no influence on the pharmacokinetics of *Motrin*.

Motrin is as effective as indomethacin in relieving arthritis pain and inflammation. *Motrin* causes significantly fewer CNS effects and about half as many GI complaints as indomethacin.

Motrin relieves pain as effectively as a combination of aspirin 650 mg plus codeine 60 mg, as documented in analgesia studies.

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Motrin is rapidly metabolized and does not accumulate. *Motrin* provides better control of therapy, rapid response to dosage adjustment, and permits tailoring dosage to each patient's needs.

New: The Motrin Patient Brochure
An easy-to-read booklet, provided to physicians, that helps patients understand their arthritis therapy... encourages their cooperation.

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The confidence that comes from experience...good reason to prescribe

Motrin® 600 mg TABLETS
(ibuprofen)

One tablet t.i.d.

Please turn page for a brief summary of prescribing information.

Upjohn The Upjohn Company
Kalamazoo, Michigan 49001

Motrin® Tablets (ibuprofen)

Contraindications: Anaphylactoid reactions have occurred in individuals hypersensitive to *Motrin* Tablets or with the syndrome of nasal polyps, angioedema and bronchospastic reactivity to aspirin, iodides, or other nonsteroidal anti-inflammatory agents.

Warnings: Peptic ulceration and GI bleeding, sometimes severe, have been reported. Ulceration, perforation and bleeding may end fatally. An association has not been established. Use *Motrin* Tablets under close supervision in patients with a history of upper gastrointestinal tract disease, after consulting ADVERSE REACTIONS. In patients with active peptic ulcer and active rheumatoid arthritis, try nonulcerogenic drugs, such as gold. If *Motrin* Tablets are used, observe the patient closely for signs of ulcer perforation or GI bleeding.

Chronic studies in rats and monkeys have shown mild renal toxicity with papillary edema and necrosis. Renal papillary necrosis has rarely been shown in humans treated with *Motrin* Tablets.

Precautions: Blurred and/or diminished vision, scotomata, and/or changes in color vision have been reported. If these develop, discontinue *Motrin* Tablets and the patient should have an ophthalmologic examination, including central visual fields and color vision testing.

Fluid retention and edema have been associated with *Motrin* Tablets; use with caution in patients with a history of cardiac decompensation or hypertension. In patients with renal impairment, reduced dosage may be necessary. Prospective studies of *Motrin* Tablets safety in patients with chronic renal failure have not been done.

Motrin Tablets can inhibit **platelet aggregation** and prolong bleeding time. Use with caution in persons with intrinsic coagulation defects and on anticoagulant therapy.

Patients should report signs or symptoms of **gastrointestinal ulceration** or bleeding, skin rash, weight gain, or edema.

Patients on prolonged **corticosteroid therapy** should have therapy tapered slowly when *Motrin* Tablets are added.

The antipyretic, anti-inflammatory activity of *Motrin* Tablets may mask inflammation and fever.

As with other nonsteroidal anti-inflammatory drugs, borderline elevations of liver tests may occur in up to 15% of patients. These abnormalities may progress, may remain essentially unchanged, or may be transient with continued therapy. Meaningful elevations of SGPT or SGOT (AST) occurred in controlled clinical trials in less than 1% of patients. Severe hepatic reactions, including jaundice and cases of fatal hepatitis, have been reported with ibuprofen as with other nonsteroidal anti-inflammatory drugs. If liver disease develops or if systemic manifestations occur (e.g. eosinophilia, rash, etc.), *Motrin* should be discontinued.

Drug interactions. *Aspirin:* used concomitantly may decrease *Motrin* blood levels.

Coumarin: bleeding has been reported in patients taking *Motrin* and coumarin.

Pregnancy and nursing mothers: *Motrin* should not be taken during pregnancy or by nursing mothers.

Adverse Reactions: The most frequent type of adverse reaction occurring with *Motrin* is gastrointestinal of which one or more occurred in 4% to 16% of the patients.

Incidence Greater than 1% (but less than 3%)—Probable Causal Relationship

Gastrointestinal: Nausea,* epigastric pain,* heartburn,* diarrhea, abdominal distress, nausea and vomiting, indigestion, constipation, abdominal cramps or pain, fullness of GI tract (bloating and flatulence); **Central Nervous System:** Dizziness,* headache, nervousness; **Dermatologic:** Rash* (including maculopapular type), pruritus; **Special Senses:** Tinnitus; **Metabolic/Endocrine:** Decreased appetite; **Cardiovascular:** Edema, fluid retention (generally responds promptly to drug discontinuation; see PRECAUTIONS).

Incidence less than 1%—Probable Causal Relationship**

Gastrointestinal: Gastric or duodenal ulcer with bleeding and/or perforation, gastrointestinal hemorrhage, melena, gastritis, hepatitis, jaundice, abnormal liver function tests; **Central Nervous System:** Depression, insomnia, confusion, emotional lability, somnolence, aseptic meningitis with fever and coma; **Dermatologic:** Vesiculobullous eruptions, urticaria, erythema multiforme, Stevens-Johnson syndrome, alopecia; **Special Senses:** Hearing loss, amblyopia (blurred and/or diminished vision, scotomata, and/or changes in color vision) (see PRECAUTIONS); **Hematologic:** Neutropenia, agranulocytosis, aplastic anemia, hemolytic anemia (sometimes Coombs positive), thrombocytopenia with or without purpura, eosinophilia, decreases in hemoglobin and hematocrit; **Cardiovascular:** Congestive heart failure in patients with marginal cardiac function, elevated blood pressure, palpitations; **Allergic:** Syndrome of abdominal pain, fever, chills, nausea and vomiting; anaphylaxis; bronchospasm (see CONTRAINDICATIONS); **Renal:** Acute renal failure in patients with pre-existing significantly impaired renal function, decreased creatinine clearance, polyuria, azotemia, cystitis, hematuria; **Miscellaneous:** Dry eyes and mouth, gingival ulcer, rhinitis.

Incidence less than 1%—Causal Relationship Unknown**

Gastrointestinal: Pancreatitis; **Central Nervous System:** Paresthesias, hallucinations, dream abnormalities, pseudotumor cerebri; **Dermatologic:** Toxic epidermal necrolysis, photoallergic skin reactions; **Special Senses:** Conjunctivitis, diplopia, optic neuritis; **Hematologic:** Bleeding episodes (e.g., epistaxis, menorrhagia); **Metabolic/Endocrine:** Gynecomastia, hypoglycemic reaction; **Cardiovascular:** Arrhythmias (sinus tachycardia, sinus bradycardia); **Allergic:** Serum sickness, lupus erythematosus syndrome, Henoch-Schönlein vasculitis; **Renal:** Renal papillary necrosis.

*Reactions occurring in 3% to 9% of patients treated with *Motrin*. (Those reactions occurring in less than 3% of the patients are unmarked.)

**Reactions are classified under *"Probable Causal Relationship (PCR)"* if there has been one positive rechallenge or if three or more cases occur which might be causally related. Reactions are classified under *"Causal Relationship Unknown"* if seven or more events have been reported but the criteria for PCR have not been met.

Overdosage: In cases of acute overdosage, the stomach should be emptied. The drug is acidic and excreted in the urine so alkaline diuresis may be beneficial.

Dosage and Administration: Rheumatoid arthritis and osteoarthritis. Suggested dosage is 300, 400, or 600 mg t.i.d. or q.i.d. Do not exceed 2400 mg per day. Mild to moderate pain: 400 mg every 4 to 6 hours as necessary.

Caution: Federal law prohibits dispensing without prescription.

Motrin is a registered trademark of The Upjohn Manufacturing Company M, Barceloneta, Puerto Rico

MED B-7-S

J-3255 September 1983

Upjohn

Books Received

Books received by THE WESTERN JOURNAL OF MEDICINE *are acknowledged in this column. Selections will be made for more extensive review in the interest of readers as space permits.*

ANNUAL REVIEW OF NEUROSCIENCE—Volume 8—Editor: W. Maxwell Cowan, Salk Institute for Biological Studies; Associate Editors: Eric M. Shooter, Stanford University School of Medicine; Charles F. Stevens, Yale University School of Medicine, and Richard F. Thompson, Stanford University. Annual Reviews Inc, 4139 El Camino Way, Palo Alto, CA 94306, 1985. 603 pages, $27.

CANADIAN MEDICINE: A STUDY IN RESTRICTED ENTRY—Ronald Hamowy, PhD, Professor of History, University of Alberta. The Fraser Institute, 626 Bute St, Vancouver, British Columbia, Canada V6E 3M1, 1984. 394 pages, $14.95 (paperback), available by ordering at any bookstore in Canada, the United States and the United Kingdom.

CHRONIC EXPOSURE OF MICE TO CIGARETTE SMOKE—Final Report of Research Performed Under Contract Entitled "Smoke Inhalation Studies in Mice" between Microbiological Associates, Bethesda, MD, and the Council for Tobacco Research, USA, Inc, New York City—Project Directors: Dr Carol J. Henry, Dr Richard E. Kouri. Field, Rich & Associates, Inc, 475 Park Ave S, New York, NY 10016, 1984. 187 pages, no price given.

COMPUTER APPLICATIONS IN CLINICAL PRACTICE: AN OVERVIEW—Edited by Daniel Levinson, MD, Associate Professor of Family and Community Medicine, University of Arizona College of Medicine, Tucson. Macmillan Publishing Co, 866 Third Ave, New York, NY 10022, 1985. 318 pages, no price given.

CONTROVERSIES IN TRAUMA MANAGEMENT—Volume 6 in **CLINICS IN EMERGENCY MEDICINE**—Edited by Robert H. Dailey, MD, Clinical Associate Professor of Medicine, University of California, San Francisco, School of Medicine, and Chief, Department of Emergency Medicine, Highland General Hospital, Oakland, California, and Michael Callaham, MD, Chief, Division of Emergency Medicine, and Associate Clinical Professor of Medicine, University of California, San Francisco, School of Medicine. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1984. 247 pages, $30.

CURRENT MEDICAL DIAGNOSIS & TREATMENT—1985—Edited by Marcus A. Krupp, MD, Clinical Professor of Medicine Emeritus, Stanford University School of Medicine, Director of Research Institute, Palo Alto Medical Foundation; Milton J. Chatton, MD, Clinical Professor of Medicine Emeritus, Stanford University School of Medicine, Senior Attending Physician, Santa Clara Valley Medical Center, San Jose, Calif, Research Associate, Palo Alto Medical Foundation, and David Werdegar, MD, MPH, Professor and Chairman, Family and Community Medicine, University of California, San Francisco; with associate authors. Lange Medical Publications, Drawer L, Los Altos, CA 94022, 1985. 1,157 pages, $27.50 (softbound).

DEALING CREATIVELY WITH DEATH—A MANUAL OF DEATH EDUCATION AND SIMPLE BURIAL—10th Edition—Ernest Morgan. Celo Press, 1901 Hannah Branch Road, Burnsville, NC 28714, 1984. 154 pages, $6.50 (paperback).

THE DEPOSITION GUIDE—A Practical Handbook for Witnesses—Larry G. Johnson, JD, Seattle. Law Forum Press, 2318 Second Ave, Seattle, WA 98121, 1984. 48 pages, $7.95 each or $62.95 for 10 copies (paperback).

DRGs FOR THE RADIOLOGIST—THEIR MEANING AND IMPACT—Rosemary T. Weiner, RN, and Russell P. Caterinicchio, PhD. SLACK Inc, 6900 Grove Road, Thorofare, NY 08086, 1984. 111 pages, $19.50 (paperback).

EMERGENCY ORTHOPAEDIC RADIOLOGY—Robert J. Neviaser, MD, Professor, Department of Orthopaedic Surgery, School of Medicine and Health Sciences, George Washington University, Washington, DC; Larry S. Eisenfeld, MD, Orthopedic Associates, Fort Myers, Florida; Sam W. Wiesel, MD, Professor, and Randall J. Lewis, MD, Associate Clinical Professor, Department of Orthopaedic Surgery, School of Medicine and Health Sciences, George Washington University, Washington, DC. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1984. 273 pages, $39.

END OF AN ILLUSION—THE FUTURE OF HEALTH POLICY IN WESTERN INDUSTRIALIZED NATIONS—Edited by Jean de Kervasdoue, Deputy Secretary of Hospitals in the French Ministry of Social Affairs and National Solidarity, Paris; John R. Kimberly, Associate Professor, Departments of Management and Health Care Systems, Wharton School, University of Pennsylvania, Philadelphia, and Victor G. Rodwin, Adjunct Assistant Professor, Institute for Health Policy Studies, University of California, San Francisco, School of Medicine. University of California Press, 2120 Berkeley Way, Berkeley, CA 94720, 1985. 286 pages, $28.50.

ENDOCRINE ASPECTS OF ACUTE ILLNESS—Edited by Glenn W. Geelhoed, MD, Associate Professor of Surgery, George Washington University School of Medicine, and Director, Surgical Research, George Washington University Medical Center, Washington, DC, and Bart Chernow, MD, Associate Professor of Medicine, Uniformed Services University of the Health Sciences, and Director of Research, Critical Care Medicine Department, Naval Hospital, Bethesda, Maryland. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1984. 341 pages, $39.50.

EVERYBODY'S GUIDE TO HOMEOPATHIC MEDICINES—Stephen Cummings, FNP, and Dana Ullman, MPH. Jeremy P. Tarcher, Inc, 9110 Sunset Blvd, Los Angeles, CA 90069, 1984. 295 pages; $14.95 (cloth), $8.95 (paperback).

FREESTANDING EMERGENCY CENTERS—A GUIDE TO PLANNING, ORGANIZATION, AND MANAGEMENT—Edited by Peter M. Friend, MS, Executive Vice President and Chief Operating Officer, Lakeland Health Services and Highland Park Hospital, Highland Park, Illinois, and John M. Shiver, MHA, Associate Administrator, Sibley Memorial Hospital, Washington, DC. Aspen Systems Corp, 1600 Research Blvd, Rockville, MD 20850, 1985. 359 pages, $37.50.

GALLSTONES—Volume 4 in **CONTEMPORARY ISSUES IN GASTROENTEROLOGY**—Edited by Sidney Cohen, MD, Chief, and Roger D. Soloway, MD, Associate Chief, Gastrointestinal Section, Department of Medicine, University of Pennsylvania School of Medicine, Philadelphia. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1984. 333 pages, $55.

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WYOMING MEDICAL SOCIETY

ANNUAL MEETING AND SCIENTIFIC PROGRAM SCHEDULE

JUNE 23-26, 1985 • JACKSON LAKE LODGE, MORAN, WYOMING • GRAND TETON NATIONAL PARK

Sunday, June 23

8:30 am WMS HOUSE OF DELEGATES OPENING SESSION

1:20 pm H. HOWARD GOLDSTEIN, MD
Introduction, Classification & Pathophysiology of Diabetes

2:30 pm THOMAS SKILLMAN, MD
So How Do We Make the Diagnosis of Diabetes?

3:45 pm JULIO SANTIAGO, MD
Management of Type I Diabetes

Monday, June 24

8:30 am H. HOWARD GOLDSTEIN, MD
Management of Type II Diabetes

9:30 am PETER H. FORSHAM, MD
Diabetic Emergencies; What to Do

10:45 am JULIO SANTIAGO, MD
Detection & Treatment of Complications

Tuesday, June 25

8:30 am THOMAS SKILLMAN, MD
Management of the Pregnant Diabetic

9:30 am DAVID HOLMES, MD
The Emotional Burden of Diabetes; Patient & Physician

10:45 am PETER H. FORSHAM, MD
New Horizons in Diabetes Research

8:00 pm PRESIDENT'S BANQUET
Guest Speaker: Joseph F. Boyle, MD, President, American Medical Association

Wednesday, June 26

9:00 am WMS HOUSE OF DELEGATES CLOSING SESSION

Faculty

Peter H. Forsham, MD, Professor of Medicine and Pediatrics, University of California, San Francisco, School of Medicine.

H. Howard Goldstein, MD, Lecturer in Medicine, Harvard Medical School, Vice President, Massachusetts Diabetes Association, Chestnut Hill, Massachusetts

David Holmes, MD, Chief of Psychiatric Service, Veterans Administration Hospital, Boston

Julio Santiago, MD, Professor of Medicine and Pediatrics, Washington University School of Medicine, St. Louis

Thomas Skillman, MD, Professor Emeritus, Ohio State University College of Medicine, Columbus

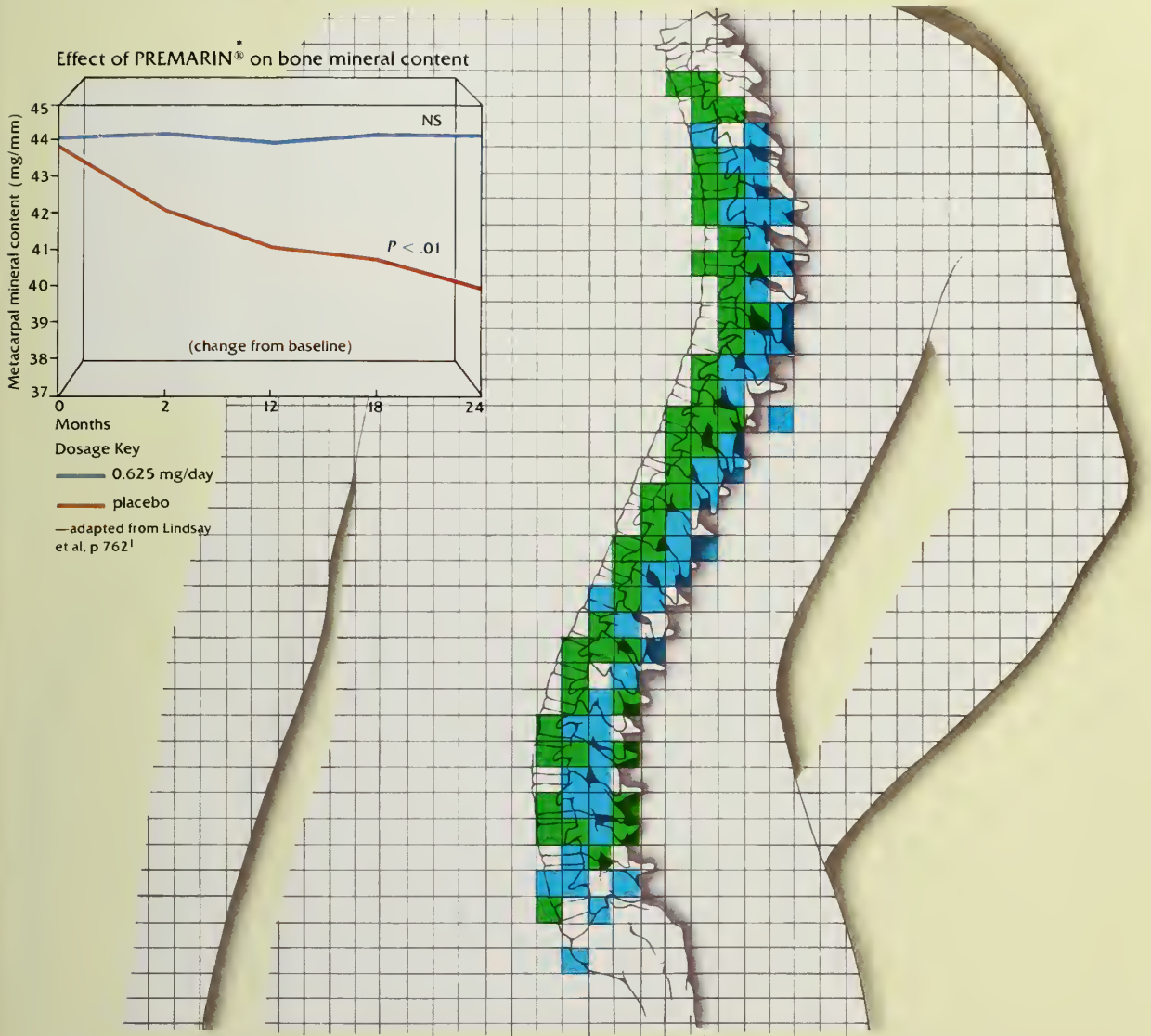
Eric J. Wedell, MD, Moderator, Endocrinologist, Internal Medicine Clinic, Cheyenne

WYOMING Medical Society

For Reservations and Information Contact:

WYOMING MEDICAL SOCIETY
P.O. Box 4009
Cheyenne, WY 82003-4009
Phone (307) 635-2424

POSTMENOPAUSAL BONE LOSS THAT INCAPACITATES



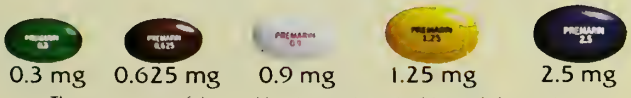
PREMARIN MAY HALT THE DISABLING COURSE OF OSTEOPOROSIS*

Osteoporosis has an enormous epidemiological impact: it affects 10 million American women, and 26% of all women over age 60.[2] The disease begins silently and progresses inexorably for 15 to 20 years, until disabling complications occur.[3]

To minimize osteoporotic damage, the condition must be detected early and treated promptly. For many patients, PREMARIN is optimal therapy for osteoporosis, as part of a comprehensive program that includes exercise, good nutrition, and calcium supplements. In a controlled study of postmenopausal and oophorectomized women, PREMARIN (Conjugated Estrogens Tablets, U.S.P.) doses of 0.625 mg/day prevented loss of metacarpal mineral content (see graph above).

PREMARIN®

(CONJUGATED ESTROGENS TABLETS, U.S.P.)



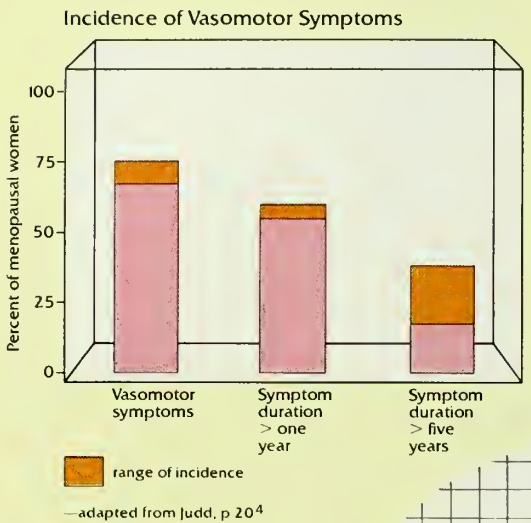
0.3 mg 0.625 mg 0.9 mg 1.25 mg 2.5 mg

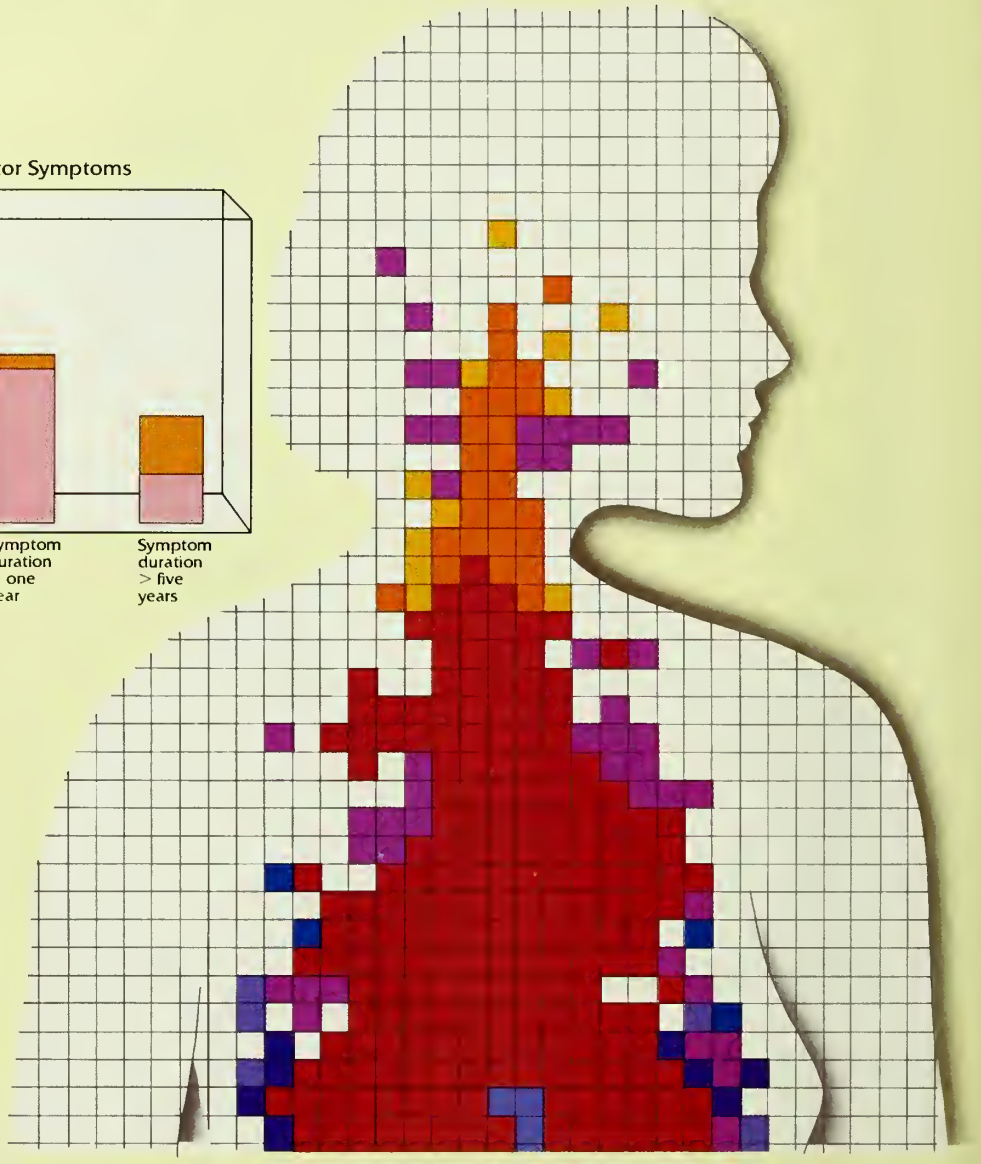
The appearance of these tablets is a trademark of Ayerst Laboratories.

*Conjugated Estrogens Tablets have been evaluated as probably effective for estrogen-deficiency-induced osteoporosis.

Please see last page for brief summary of full prescribing information.

VASOMOTOR SYMPTOMS THAT DEMAND INTERVENTION





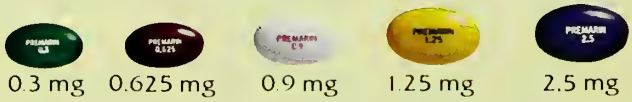
PREMARIN RELIEVES MODERATE TO SEVERE VASOMOTOR SYMPTOMS

Vasomotor symptoms are the most common manifestation of the menopause, affecting up to 75% of menopausal women. Of these, 80% may suffer for more than a year and up to 50% for more than five years.[4] These symptoms can disrupt a woman's life by chronically interrupting sleep, resulting in anxiety and irritability.

In a study of postmenopausal women suffering severe episodes of cutaneous flushing, symptoms improved markedly after administration of estrogen[5]—the treatment of choice for moderate to severe vasomotor symptoms.[6] The estrogen of choice is PREMARIN, the most widely prescribed estrogen for over 40 years. PREMARIN (Conjugated Estrogens Tablets, U.S.P.) relieves moderate to severe vasomotor symptoms of the natural menopause, as well as the acute and often severe symptoms of surgical menopause.

PREMARIN®

(CONJUGATED ESTROGENS TABLETS, U.S.P.)

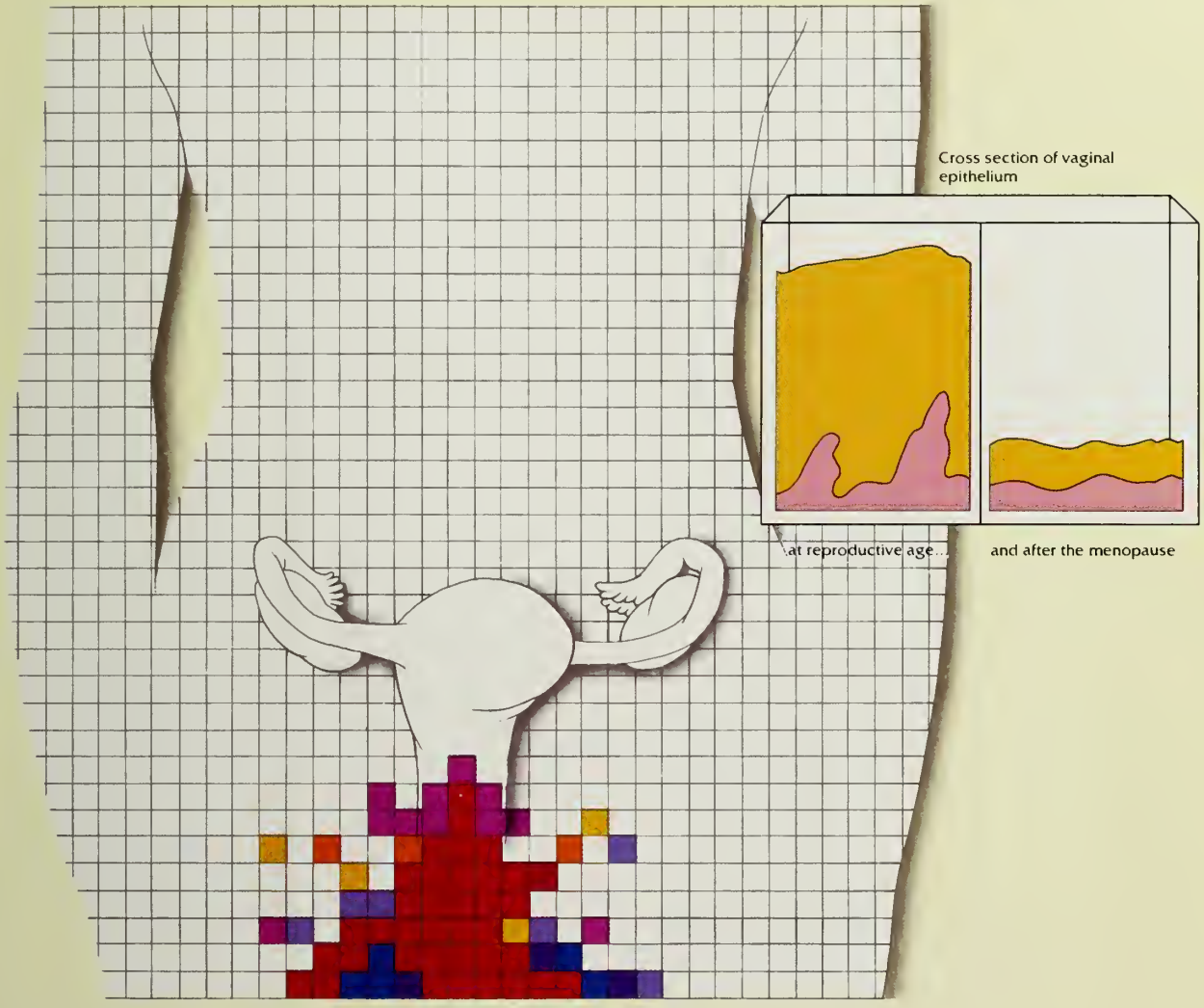


0.3 mg 0.625 mg 0.9 mg 1.25 mg 2.5 mg

The appearance of these tablets is a trademark of Ayerst Laboratories

Please see last page for brief summary of full prescribing information.

VAGINAL ATROPHY THAT INTERFERES WITH SEXUALITY



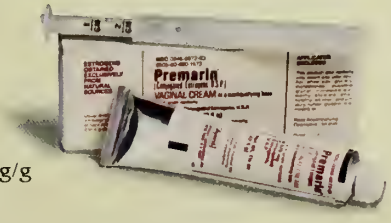
PREMARIN RESTORES THE VAGINAL ENVIRONMENT

In the postmenopausal woman, decreasing levels of estrogen can have devastating effects on a woman's sexual functioning. The pH of vaginal secretions rises, promoting the growth of contaminating organisms. The vaginal epithelium dries and thins, becoming susceptible to irritation, injury, and infection. Sexual relations may be difficult or impossible.

PREMARIN (Conjugated Estrogens, U.S.P.) Vaginal Cream focuses therapy at the site of the problem. Vaginal dryness is relieved, pH reverts to its normal acidity, and the epithelium thickens and becomes more resistant to injury and infection. With the vaginal environment returned to its premenopausal state, sexual function may improve.

PREMARIN®

(CONJUGATED ESTROGENS, U.S.P.) Vaginal Cream



0.625 mg/g

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Please see last page for brief summary of full prescribing information.

BRIEF SUMMARY *(FOR FULL PRESCRIBING INFORMATION AND PATIENT INFORMATION, SEE PACKAGE CIRCULAR)*

PREMARIN® Brand of Conjugated Estrogens Tablets, U.S.P.

PREMARIN® Brand of Conjugated Estrogens, U.S.P. Vaginal Cream in a nonliquefying base

1. ESTROGENS HAVE BEEN REPORTED TO INCREASE THE RISK OF ENDOMETRIAL CARCINOMA.

Three independent case control studies have reported an increased risk of endometrial cancer in postmenopausal women exposed to exogenous estrogens for more than one year. This risk was independent of the other known risk factors for endometrial cancer. These studies are further supported by the finding that incidence rates of endometrial cancer have increased sharply since 1969 in eight different areas of the United States with population-based cancer reporting systems, an increase which may be related to the rapidly expanding use of estrogens during the last decade. The three case control studies reported that the risk of endometrial cancer in estrogen users was about 4.5 to 13.9 times greater than in nonusers. The risk appears to depend on both duration of treatment and on estrogen dose. In view of these findings, when estrogens are used for the treatment of menopausal symptoms, the lowest dose that will control symptoms should be utilized and medication should be discontinued as soon as possible. When prolonged treatment is medically indicated, the patient should be reassessed on at least a semiannual basis to determine the need for continued therapy. Although the evidence must be considered preliminary, one study suggests that cyclic administration of low doses of estrogen may carry less risk than continuous administration; it therefore appears prudent to utilize such a regimen. Close clinical surveillance of all women taking estrogens is important. In all cases of undiagnosed persistent or recurring abnormal vaginal bleeding, adequate diagnostic measures should be undertaken to rule out malignancy. There is no evidence at present that "natural" estrogens are more or less hazardous than "synthetic" estrogens at equiestrogenic doses.

2. ESTROGENS SHOULD NOT BE USED DURING PREGNANCY.

The use of female sex hormones, both estrogens and progestogens, during early pregnancy may seriously damage the offspring. It has been shown that females exposed in utero to diethylstilbestrol, a non-steroidal estrogen, have an increased risk of developing in later life a form of vaginal or cervical cancer that is ordinarily extremely rare. This risk has been estimated as not greater than 4 per 1000 exposures. Furthermore, a high percentage of such exposed women (from 30 to 90 percent) have been found to have vaginal adenosis, epithelial changes of the vagina and cervix. Although these changes are histologically benign, it is not known whether they are precursors of malignancy. Although similar data are not available with the use of other estrogens, it cannot be presumed they would not induce similar changes. Several reports suggest an association between intrauterine exposure to female sex hormones and congenital anomalies, including congenital heart defects and limb reduction defects. One case control study estimated a 4.7-fold increased risk of limb reduction defects in infants exposed in utero to sex hormones (oral contraceptives, hormone withdrawal tests for pregnancy, or attempted treatment for threatened abortion). Some of these exposures were very short and involved only a few days of treatment. The data suggest that the risk of limb reduction defects in exposed fetuses is somewhat less than 1 per 1000. In the past, female sex hormones have been used during pregnancy in an attempt to treat threatened or habitual abortion. There is considerable evidence that estrogens are ineffective for these indications, and there is no evidence from well controlled studies that progestogens are effective for these uses. If PREMARIN is used during pregnancy, or if the patient becomes pregnant while taking this drug, she should be apprised of the potential risks to the fetus, and the advisability of pregnancy continuation.

DESCRIPTION: PREMARIN (Conjugated Estrogens, U.S.P.) contains a mixture of estrogens, obtained exclusively from natural sources, blended to represent the average composition of material derived from pregnant mares' urine. It contains estrone, equilin, and 17α-dihydroequilin, together with smaller amounts of 17α-estradiol, equilenin, and 17α-dihydroequilenin as salts of their sulfate esters.

INDICATIONS: Based on a review of PREMARIN Tablets by the National Academy of Sciences – National Research Council and/or other information, FDA has classified the indications for use as follows:

Effective: 1. Moderate to severe vasomotor symptoms associated with the menopause. (There is no evidence that estrogens are effective for nervous symptoms or depression without associated vasomotor symptoms, and they should not be used to treat such conditions.)

2. Atrophic vaginitis.
3. Kraurosis vulvae.
4. Female hypogonadism.
5. Female castration.
6. Primary ovarian failure.
7. Breast cancer (for palliation only) in appropriately selected women and men with metastatic disease.
8. Prostatic carcinoma – palliative therapy of advanced disease.
9. Postpartum breast engorgement – Although estrogens have been widely used for the prevention of postpartum breast engorgement, controlled studies have demonstrated that the incidence of significant painful engorgement in patients not receiving such hormonal therapy is low and usually responsive to appropriate analgesic or other supportive therapy. Consequently, the benefit to be derived from estrogen therapy for this indication must be carefully weighed against the potential increased risk of puerperal thromboembolism associated with the use of large doses of estrogens.

PREMARIN HAS NOT BEEN SHOWN TO BE EFFECTIVE FOR ANY PURPOSE DURING PREGNANCY AND ITS USE MAY CAUSE SEVERE HARM TO THE FETUS (SEE BOXED WARNING).

"Probably" effective: For estrogen deficiency-induced osteoporosis, and only when used in conjunction with other important therapeutic measures such as diet, calcium, physiotherapy, and good general health-promoting measures. Final classification of this indication requires further investigation.

INDICATIONS: PREMARIN (Conjugated Estrogens, U.S.P.) Vaginal Cream is indicated in the treatment of atrophic vaginitis and kraurosis vulvae. PREMARIN Vaginal Cream HAS NOT BEEN SHOWN TO BE EFFECTIVE FOR ANY PURPOSE DURING PREGNANCY AND ITS USE MAY CAUSE SEVERE HARM TO THE FETUS (SEE BOXED WARNING).

CONTRAINDICATIONS: Estrogens should not be used in women (or men) with any of the following conditions: 1. Known or suspected cancer of the breast except in appropriately selected patients being treated for metastatic disease. 2. Known or suspected estrogen-dependent neoplasia. 3. Known or suspected pregnancy (See Boxed Warning). 4. Undiagnosed abnormal genital bleeding. 5. Active thrombophlebitis or thromboembolic disorders. 6. A past history of thrombophlebitis, thrombosis, or thromboembolic disorders associated with previous estrogen use (except when used in treatment of breast or prostatic malignancy).

WARNINGS: Long term continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, cervix, vagina, and liver. There are now reports that estrogens increase the risk of carcinoma of the endometrium in humans. (See Boxed Warning.) At the present time there is no satisfactory evidence that estrogens given to postmenopausal women increase the risk of cancer of the breast, although a recent study has raised this possibility. There is a need for caution in prescribing estrogens for women with a strong family history of breast cancer or who have breast nodules, fibrocystic disease, or abnormal mammograms. A recent study has reported a 2- to 3-fold increase in the risk of surgically confirmed gallbladder disease in women receiving postmenopausal estrogens.

Adverse effects of oral contraceptives may be expected at the larger doses of estrogen used to treat prostatic or breast cancer or postpartum breast engorgement, it has been shown that there is an increased risk of thrombosis in men receiving estrogens for prostatic cancer and women for postpartum breast engorgement. Users of oral contraceptives have an increased risk of diseases, such as thrombophlebitis, pulmonary embolism, stroke, and myocardial infarction. Cases of retinal thrombosis, mesenteric thrombosis, and optic neuritis have been reported in oral contraceptive users. An increased risk of postsurgery thromboembolic complications has also been reported in users of oral contraceptives. If feasible, estrogen should be discontinued at least 4 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization. Estrogens should not be used in persons with active thrombophlebitis, thromboembolic disorders, or in persons with a history of such disorders in association with estrogen use. They should be used with caution in patients with cerebral vascular or coronary artery disease. Large doses (5 mg conjugated estrogens per day), comparable to those used to treat cancer of the prostate and breast have been shown to increase the risk of nonfatal myocardial infarction, pulmonary embolism and thrombophlebitis. When doses of this size are used, any of the thromboembolic and thrombotic adverse effects should be considered a clear risk.

Benign hepatic adenomas should be considered in estrogen users having abdominal pain and tenderness, abdominal mass, or hypovolemic shock. Hepatocellular carcinoma has been reported in women taking estrogen-containing oral contraceptives. Increased blood pressure may occur with use of estrogens in the menopause and blood pressure should be monitored with estrogen use. A worsening of glucose tolerance has been observed in patients on estrogen-containing oral contraceptives. For this reason, diabetic patients should be carefully observed. Estrogens may lead to severe hypercalcemia in patients with breast cancer and bone metastases.

PRECAUTIONS: Physical examination and a complete medical and family history should be taken prior to the initiation of any estrogen therapy with special reference to blood pressure, breasts, abdomen, and pelvic organs, and should include a Papanicolau smear. As a general rule, estrogen should not be prescribed for longer than one year without another physical examination being performed. Conditions influenced by fluid retention such as asthma, epilepsy, migraine, and cardiac or renal dysfunction, require careful observation. Certain patients may develop manifestations of excessive estrogenic stimulation, such as abnormal or excessive uterine bleeding, mastodynia, etc. Prolonged administration of unopposed estrogen therapy has been reported to increase the risk of endometrial hyperplasia in some patients. Oral contraceptives appear to be associated with an increased incidence of mental depression. Patients with a history of depression should be carefully observed. Preexisting uterine leiomyomata may increase in size during estrogen use. The pathologist should be advised of estrogen therapy when relevant specimens are submitted. If jaundice develops in any patient receiving estrogen, the medication should be discontinued while the cause is investigated. Estrogens should be used with care in patients with impaired liver function, renal insufficiency, metabolic bone diseases associated with hypercalcemia, or in young patients in whom bone growth is not complete.

The following changes may be expected with larger doses of estrogen:

a. Increased sulfobromophthalein retention.

b. Increased prothrombin and factors VII, VIII, IX, and X, decreased antithrombin 3, increased norepinephrine-induced platelet aggregability.

c. Increased thyroid binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by PBI, T4 by column, or T4 by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG; free T4 concentration is unaltered.

d. Impaired glucose tolerance.

e. Decreased pregnanediol excretion.

f. Reduced response to metyrapone test.

g. Reduced serum folate concentration.

h. Increased serum triglyceride and phospholipid concentration.

As a general principle, the administration of any drug to nursing mothers should be done only when clearly necessary since many drugs are excreted in human milk.

ADVERSE REACTIONS: The following have been reported with estrogenic therapy, including oral contraceptives: breakthrough bleeding; spotting; change in menstrual flow; dysmenorrhea; premenstrual-like syndrome; amenorrhea during and after treatment; increase in size of uterine fibromyomata; vaginal candidiasis; change in cervical erosion and in degree of cervical secretion; cystitis-like syndrome; tenderness, enlargement, secretion (of breasts); nausea, vomiting, abdominal cramps, bloating; cholestatic jaundice; chloasma or melasma which may persist when drug is discontinued; erythema multiforme; erythema nodosum; hemorrhagic eruption; loss of scalp hair; hirsutism; steepening of corneal curvature; intolerance to contact lenses; headache, migraine, dizziness, mental depression, chorea; increase or decrease in weight; reduced carbohydrate tolerance; aggravation of porphyria; edema; changes in libido.

ACUTE OVERDOSAGE: May cause nausea, and withdrawal bleeding may occur in females.

DOSAGE AND ADMINISTRATION:

PREMARIN® Brand of Conjugated Estrogens Tablets, U.S.P.

1. *Given cyclically for short-term use only:* For treatment of moderate to severe *vasomotor* symptoms, atrophic vaginitis, or kraurosis vulvae associated with the menopause (0.3 to 1.25 mg or more daily).

The lowest dose that will control symptoms should be chosen and medication should be discontinued as promptly as possible.

Administration should be cyclic (e.g., three weeks on and one week off).

Attempts to discontinue or taper medication should be made at three to six month intervals.

2. *Given cyclically:* Female hypogonadism, Female castration, Primary ovarian failure, Osteoporosis.

Female hypogonadism – 2.5 to 7.5 mg daily, in divided doses for 20 days, followed by a rest period of 10 days' duration. If bleeding does not occur by the end of this period, the same dosage schedule is repeated. The number of courses of estrogen therapy necessary to produce bleeding may vary depending on the responsiveness of the endometrium.

If bleeding occurs before the end of the 10 day period, begin a 20 day estrogen-progestin cyclic regimen with PREMARIN (Conjugated Estrogens Tablets, U.S.P.), 2.5 to 7.5 mg daily in divided doses, for 20 days. During the last five days of estrogen therapy, give an oral progestin. If bleeding occurs before this regimen is concluded, therapy is discontinued and may be resumed on the fifth day of bleeding.

Female castration and primary ovarian failure – 1.25 mg daily, cyclically. Adjust upward or downward according to response of the patient. For maintenance, adjust dosage to lowest level that will provide effective control.

Osteoporosis (to retard progression) – 1.25 mg daily, cyclically.

3. *Given for a few days:* Prevention of postpartum breast engorgement – 3.75 mg every four hours for five doses, or 1.25 mg every four hours for five days.

4. *Given chronically:* Inoperable progressing prostatic cancer – 1.25 to 2.5 mg three times daily.

Inoperable progressing breast cancer in appropriately selected men and postmenopausal women – 10 mg three times daily for a period of at least three months.

Patients with an intact uterus should be monitored for signs of endometrial cancer and appropriate measures taken to rule out malignancy in the event of persistent or recurring abnormal vaginal bleeding.

PREMARIN® Brand of Conjugated Estrogens, U.S.P. Vaginal Cream

Given cyclically for short-term use only: For treatment of atrophic vaginitis or kraurosis vulvae.

The lowest dose that will control symptoms should be chosen and medication should be discontinued as promptly as possible.

Administration should be cyclic (e.g., three weeks on and one week off).

Attempts to discontinue or taper medication should be made at three to six month intervals.

Usual dosage range: 2 to 4 g daily, intravaginally or topically, depending on the severity of the condition.

Treated patients with an intact uterus should be monitored closely for signs of endometrial cancer and appropriate diagnostic measures should be taken to rule out malignancy in the event of persistent or recurring abnormal vaginal bleeding.

HOW SUPPLIED: PREMARIN (Conjugated Estrogens Tablets, U.S.P.). No. B65 – Each *purple* tablet contains 2.5 mg in bottles of 100 and 1,000. No. B66 – Each *yellow* tablet contains 1.25 mg in bottles of 100 and 1,000. Also in Cycle Pack of 21 and in unit dose package of 100. No. B64 – Each *white* tablet contains 0.9 mg in bottles of 100. Also in Cycle Pack of 21. No. B67 – Each *maroon* tablet contains 0.625 mg in bottles of 100 and 1,000. Also in Cycle Pack of 21 and unit dose package of 100. No. B68 – Each *green* tablet contains 0.3 mg in bottles of 100 and 1,000. The appearance of these tablets is a trademark of Ayerst Laboratories.

PREMARIN (Conjugated Estrogens, U.S.P.) Vaginal Cream – No. B72 – Each gram contains 0.625 mg Conjugated Estrogens, U.S.P. (Also contains cetyl esters wax, cetyl alcohol, white wax, glyceryl monostearate, propylene glycol monostearate, methyl stearate, phenylethyl alcohol, sodium lauryl sulfate, glycerin, and mineral oil.)

Combination package: Each contains Net Wt. 1½ oz. (42.5 g) tube with one calibrated plastic applicator.

Also Available – Refill package: Each contains Net Wt. 1½ oz. (42.5 g) tube. 4340R1/285

References: 1. Lindsay R, Hart DM, Clark DM: The minimum effective dose of estrogen for prevention of postmenopausal bone loss. *Obstet Gynecol* 1984,63:759-763. **2.** Katz WA: *Rheumatic Diseases. Diagnosis and Management*. Philadelphia, JB Lippincott Co, 1977, p 672. **3.** Reese WD: A better way to screen for osteoporosis. *Contemp Ob/Gyn* 1983,22(November):116-131. **4.** Judd HL: After the menopause. *Transition* 1983;1:19-30. **5.** Erlik Y, Tataryn IV, Meldrum DR, et al: Association of waking episodes with menopausal hot flushes. *JAMA* 1981,245:1741-1744. **6.** Meldrum DR: The pathophysiology of postmenopausal symptoms. *Sem Reprod Endocrinol* 1983;1(February):11-17.

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700 **Pharmacotherapy of Asthma**
DEAN SHEPPARD, MD
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703 **A Survey of Patient Satisfaction, Knowledge and Compliance**
PAUL J. SANAZARO, MD
Dr Sanazaro is a private consultant in health services research and development and Clinical Professor of Medicine, University of California, San Francisco, School of Medicine.

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706 **Autopsies by Primary Practitioners—A Solution to the Decline in Autopsies?**
STEPHEN H. KRIEBEL, MD
Dr Kriebel is in family practice in Forks, Washington.

708 **The Return of Two-Class Medicine—Ill Effects of Medi-Cal Reform**
HOWARD WAITZKIN, MD, PhD
Dr Waitzkin is Professor of Medicine and Social Sciences and Chief of the Division of General Internal Medicine and Primary Care at the University of California, Irvine.

PUBLIC HEALTH AND PREVENTIVE MEDICINE

710 **Thirty-seven Miles Up Highway 70**
LAWRENCE J. COHEN, MD, MPH, and JIMM MURRAY, REMTA
Dr Cohen is Administrator, Wyoming Division of Health and Medical Services, and Mr Murray is Director, Emergency Medical Services, Wyoming Division of Health and Medical Services, Cheyenne.

MEDICAL SCHOOLS OF THE WEST

712 **The UCLA School of Medicine**
C. S. BLAND
Ms Bland is administrative analyst on the staff of Sherman M. Mellinkoff, MD, Dean of the UCLA School of Medicine, Los Angeles.

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717 **The Absence of Hematuria in Patients With Symptomatic Urinary Tract Stones**
PATRICK M. DUNN, MD; ROBERT T. KELLER, MD, and STEPHEN R. JONES, MD
From the Department of Medicine, Good Samaritan Hospital and Medical Center, Portland.

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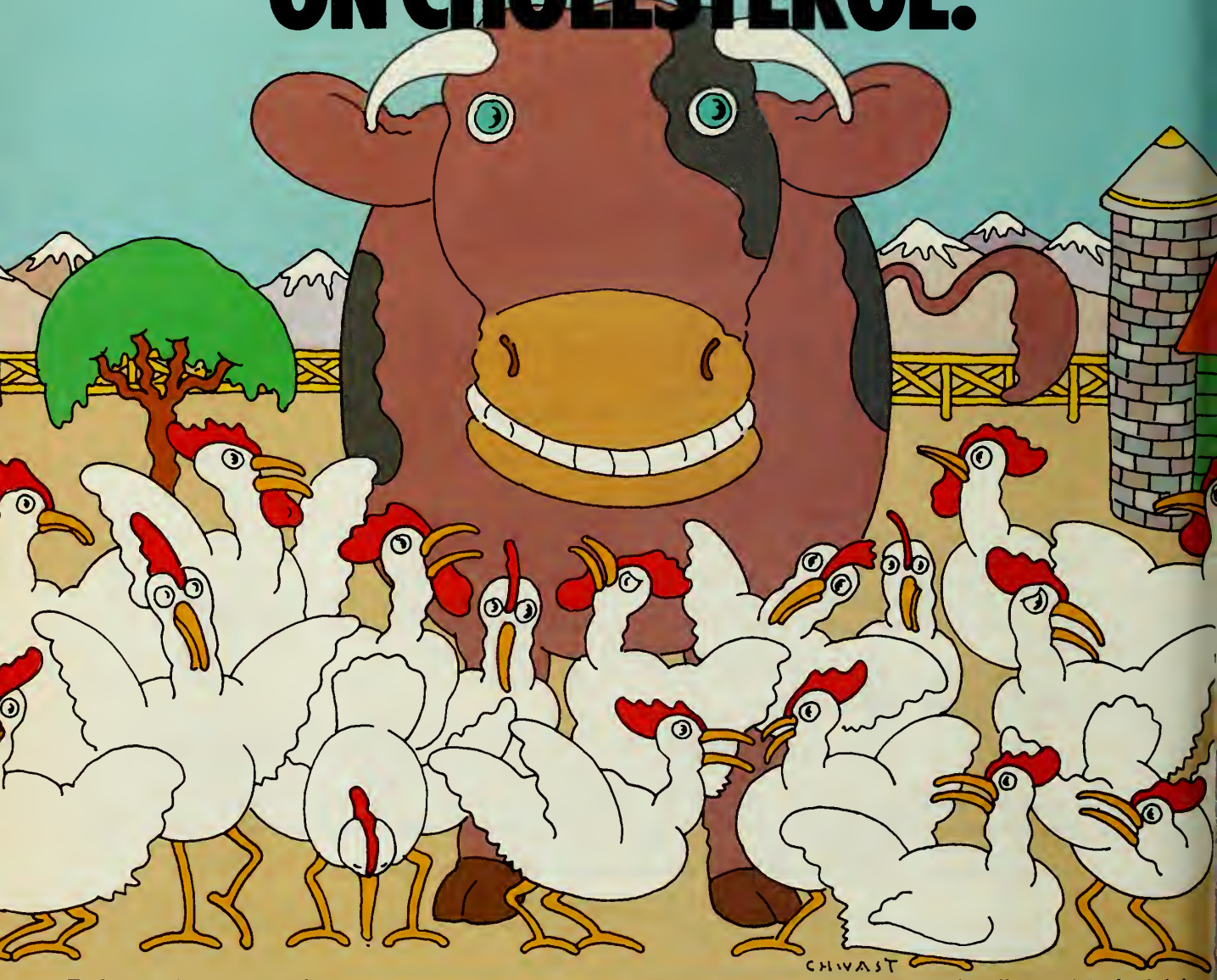
★ **Affiliated Clinical Investigation Societies: the Western Association of Physicians; the Western Society for Clinical Investigation; the Western Section, American Federation for Clinical Research; the Western Society for Pediatric Research; the Western Region, Society for Investigative Dermatology.**

ANNOUNCING SOME NEW FINDINGS ON CHOLESTEROL.



Perhaps rather surprisingly, beef has no more cholesterol than chicken. Even roast chicken without skin.

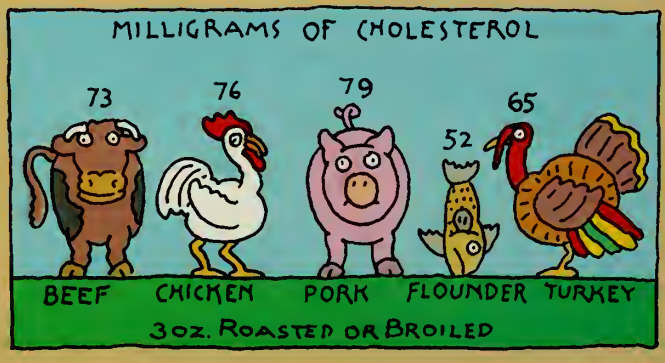
That was the finding of a new U.S.D.A. study on beef nutrient composition.*

That same study found beef is lower in calories than ever.

And lower in fat.

In fact, three ounces of beef now has just 192 calories and a modest nine grams of fat, over half of which is unsaturated.

Today, new breeding and feeding techniques are making beef a whole different animal. Though not so different that it isn't still one of the body's best sources of iron, zinc, B-vitamins and protein.



It all means moderate portions of beef can fit easily into a reduced cholesterol, low saturated fat diet.

And that can stop a lot of squawking when you recommend one.

For more information on the new U.S.D.A. study and beef's contribution to healthy eating in the eighties, write to Beef Nutrition, California Beef Council, 551 Foster City Boulevard, Suite A, Foster City, California 94404.

*Beef data from 1983 Beef Nutritive Composition Studies conducted by the U.S.D.A. and National Live Stock and Meat Board.

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Continuing Medical Education

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CALIFORNIA, HAWAII AND NEVADA

This listing of continuing education programs in California, Hawaii and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Department of Continuing Medical Education, California Medical Association, 44 Gough St., San Francisco 94103; or phone (415) 863-5522. For a list of organizations approved for Category I credit toward the CMA Certificate in Continuing Medical Education or for more information on accreditation or certification, please write to the above address.

ANESTHESIOLOGY

May 17-22—**Anesthesiology Review Course.** UCSD at Vacation Village, San Diego. Friday-Wednesday. 38 hrs.

June 6-9—**California Society of Anesthesiologists Annual Scientific Meeting** at Hilton Hotel, San Francisco. Thursday-Sunday. 17 hrs. Contact: CSA, 100 S. Ellsworth Ave., Ste. 806, San Mateo 94401. (415) 348-1407.

CARDIOLOGY

May 18—**The Richard J. Bing Symposium IV Heart Transplantation: A Therapeutic Option.** Huntington Memorial Hospital, Pasadena. Saturday. Fee: $50. Contact: Medical Staff Coordinator, Huntington Memorial Hospital, 100 Congress St., Pasadena, CA 91105. (818) 440-5165.

May 21—**Cardiac Rehabilitation Update: Diet and Exercise.** American Heart Association at Orthopedic Hospital, Los Angeles. Tuesday. Contact: Karen Bodziak, American Heart Association, Los Angeles, CA 90057. (213) 385-4231, ext. 60.

June 16-20—**Western Thoracic Surgical Association Annual Meeting** at Hyatt Lake Tahoe, Incline Village. Sunday-Thursday. Contact: WTSA, 13 Elm St., Manchester, MA 01944. (617) 927-8330.

June 21-23—**Diagnosis and Management of the Acute M.I.** International Medical Education Corp. at Hyatt Regency, Lake Tahoe. Friday-Sunday. 13 hrs. Fee: $295. Contact: IMEC, 64 Inverness Dr. E., Englewood, CO 80112.

June 25-27—**Vascular and Pulmonary Disease: Diagnosis and Management.** Medical Education Resources at Balboa Bay Club, Newport Beach. Tuesday-Thursday. 13 hrs. Fee: $275. Contact: Mrs Leslie Shaffer, Medical Education Resources, 5808 S. Rapp St., Ste. 202, Littleton, CO 80120. (303) 798-9682.

June 26-28—**Consultative Cardiology: Update in Diagnostic and Therapeutic Techniques.** American College of Cardiology at Westin South Coast Plaza, Costa Mesa. Wednesday-Friday. Contact: American College of Cardiology, 9111 Old Georgetown Rd., Bethesda, MD 20814.

June 28-30—**ECG Interpretation and Arrhythmia Management.** International Medical Education Corp. at Disneyland Hotel, Anaheim. Friday-Sunday. 13 hrs. Fee: $295. Contact: IMEC, 64 Inverness Dr. E, Englewood, CO 80112.

July 1-3—**Cardiac Morphology: Angiographic, Auscultatory, Echocardiographic and Electrocardiographic Correlations.** American College of Cardiology at Incline Village, Nevada. Monday-

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KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 44 Gough Street, San Francisco 94103. (415) 863-5522.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Flora Harlee-Cordett, MS, MPH, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr., MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, ext. 2400.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 563-4321, ext. 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 497-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0328.

UCI: University of California, Irvine
Contact: E. R. Jennings, MD, Assistant Dean, University of California, Irvine, California College of Medicine, c/o UCI/CME Program, Memorial Hospital Medical Center, 2801 Atlantic Avenue, Long Beach 90801. (213) 595-3837, or (714) 856-5414, UCI Extension.

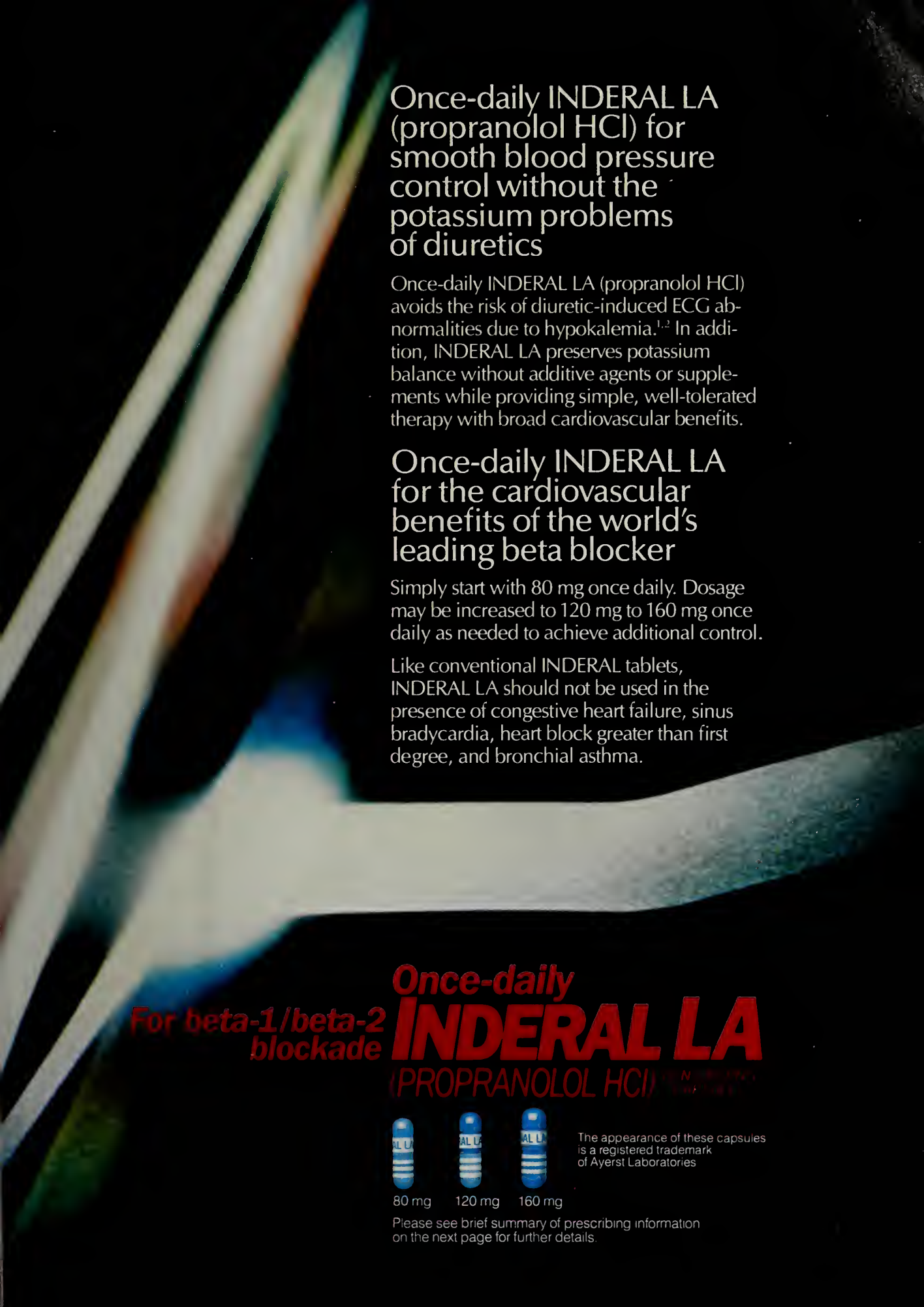
UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 452-3940.

UCSF: University of California, San Francisco
Contact: David S. Gullion, MD, Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 224-7051.

Right from the start in hypertension...



Once-daily INDERAL LA (propranolol HCl) for smooth blood pressure control without the potassium problems of diuretics

Once-daily INDERAL LA (propranolol HCl) avoids the risk of diuretic-induced ECG abnormalities due to hypokalemia.[1,2] In addition, INDERAL LA preserves potassium balance without additive agents or supplements while providing simple, well-tolerated therapy with broad cardiovascular benefits.

Once-daily INDERAL LA for the cardiovascular benefits of the world's leading beta blocker

Simply start with 80 mg once daily. Dosage may be increased to 120 mg to 160 mg once daily as needed to achieve additional control.

Like conventional INDERAL tablets, INDERAL LA should not be used in the presence of congestive heart failure, sinus bradycardia, heart block greater than first degree, and bronchial asthma.

For beta-1/beta-2 blockade

Once-daily INDERAL LA

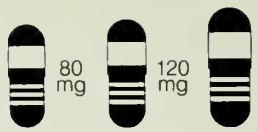
(PROPRANOLOL HCl)

80 mg 120 mg 160 mg

The appearance of these capsules is a registered trademark of Ayerst Laboratories

Please see brief summary of prescribing information on the next page for further details.

Once-daily
For beta-1/beta-2 blockade INDERAL® LA
(PROPRANOLOL HCl) LONG ACTING CAPSULES



The appearance of these capsules is a registered trademark of Ayerst Laboratories

BRIEF SUMMARY *(FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE CIRCULAR.)*

INDERAL® LA brand of propranolol hydrochloride **(Long Acting Capsules)**

DESCRIPTION. Inderal LA is formulated to provide a sustained release of propranolol hydrochloride. Inderal LA is available as 80 mg, 120 mg, and 160 mg capsules.

CLINICAL PHARMACOLOGY. INDERAL is a nonselective beta-adrenergic receptor blocking agent possessing no other autonomic nervous system activity. It specifically competes with beta-adrenergic receptor stimulating agents for available receptor sites. When access to beta-receptor sites is blocked by INDERAL, the chronotropic, inotropic, and vasodilator responses to beta-adrenergic stimulation are decreased proportionately.

INDERAL LA Capsules (80, 120, and 160 mg) release propranolol HCl at a controlled and predictable rate. Peak blood levels following dosing with INDERAL LA occur at about 6 hours and the apparent plasma half-life is about 10 hours. When measured at steady state over a 24-hour period the areas under the propranolol plasma concentration-time curve (AUCs) for the capsules are approximately 60% to 65% of the AUCs for a comparable divided daily dose of INDERAL tablets. The lower AUCs for the capsules are due to greater hepatic metabolism of propranolol, resulting from the slower rate of absorption of propranolol. Over a twenty-four (24) hour period, blood levels are fairly constant for about twelve (12) hours then decline exponentially.

INDERAL LA should not be considered a simple mg for mg substitute for conventional propranolol and the blood levels achieved do not match (are lower than) those of two to four times daily dosing with the same dose. When changing to INDERAL LA from conventional propranolol, a possible need for retitration upwards should be considered especially to maintain effectiveness at the end of the dosing interval. In most clinical settings, however, such as hypertension or angina where there is little correlation between plasma levels and clinical effect, INDERAL LA has been therapeutically equivalent to the same mg dose of conventional INDERAL as assessed by 24-hour effects on blood pressure and on 24-hour exercise responses of heart rate, systolic pressure and rate pressure product. INDERAL LA can provide effective beta blockade for a 24-hour period.

The mechanism of the antihypertensive effect of INDERAL has not been established. Among the factors that may be involved in contributing to the antihypertensive action are (1) decreased cardiac output, (2) inhibition of renin release by the kidneys, and (3) diminution of tonic sympathetic nerve outflow from vasomotor centers in the brain. Although total peripheral resistance may increase initially, it readjusts to or below the pretreatment level with chronic use. Effects on plasma volume appear to be minor and somewhat variable. INDERAL has been shown to cause a small increase in serum potassium concentration when used in the treatment of hypertensive patients.

In angina pectoris, propranolol generally reduces the oxygen requirement of the heart at any given level of effort by blocking the catecholamine-induced increases in the heart rate, systolic blood pressure, and the velocity and extent of myocardial contraction. Propranolol may increase oxygen requirements by increasing left ventricular fiber length, end diastolic pressure and systolic ejection period. The net physiologic effect of beta-adrenergic blockade is usually advantageous and is manifested during exercise by delayed onset of pain and increased work capacity.

In dosages greater than required for beta blockade, INDERAL also exerts a quinidine-like or anesthetic-like membrane action which affects the cardiac action potential. The significance of the membrane action in the treatment of arrhythmias is uncertain.

The mechanism of the antimigraine effect of propranolol has not been established. Beta-adrenergic receptors have been demonstrated in the pial vessels of the brain.

Beta receptor blockade can be useful in conditions in which, because of pathologic or functional changes, sympathetic activity is detrimental to the patient. But there are also situations in which sympathetic stimulation is vital. For example, in patients with severely damaged hearts, adequate ventricular function is maintained by virtue of sympathetic drive which should be preserved. In the presence of AV block, greater than first degree, beta blockade may prevent the necessary facilitating effect of symoathetic activity on conduction. Beta blockade results in bronchial constriction by interfering with adrenergic bronchodilator activity which should be preserved in patients subject to bronchospasm.

Propranolol is not significantly dialyzable.

INDICATIONS AND USAGE. Hypertension: INDERAL LA is indicated in the management of hypertension; it may be used alone or used in combination with other antihypertensive agents, particularly a thiazide diuretic. INDERAL LA is not indicated in the management of hypertensive emergencies.

Angina Pectoris Due to Coronary Atherosclerosis: INDERAL LA is indicated for the long-term management of patients with angina pectoris.

Migraine: INDERAL LA is indicated for the prophylaxis of common migraine headache. The efficacy of propranolol in the treatment of a migraine attack that has started has not been established and propranolol is not indicated for such use.

Hypertrophic Subaortic Stenosis: INDERAL LA is useful in the management of hypertrophic subaortic stenosis, especially for treatment of exertional or other stress-induced angina, palpitations, and syncope. INDERAL LA also improves exercise performance. The effectiveness of propranolol hydrochloride in this disease appears to be due to a reduction of the elevated outflow pressure gradient which is exacerbated by beta-receptor stimulation. Clinical improvement may be temporary.

CONTRAINDICATIONS. INDERAL is contraindicated in 1) cardiogenic shock, 2) sinus bradycardia and greater than first degree block, 3) bronchial asthma, 4) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL.

WARNINGS. CARDIAC FAILURE. Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta blockade may precipitate more severe failure. Although beta blockers should be avoided in overt congestive heart failure, if necessary, they can be used with close follow-up in patients with a history of failure who are well compensated and are receiving digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle.

IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta blockers can, in some cases, lead to cardiac failure. Therefore, at the first sign or symptom of heart failure, the patient should be digitalized and/or treated with diuretics, and the response observed closely; or INDERAL should be discontinued (gradually, if possible).

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following abrupt discontinuance of INDERAL therapy. Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced over at least a few weeks, and the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)— PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

MAJOR SURGERY. The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

INDERAL (propranolol HCl), like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in starting and maintaining the heartbeat has also been reported with beta blockers.

DIABETES AND HYPOGLYCEMIA. Beta-adrenergic blockade may prevent the appearance of certain premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia in labile insulin-dependent diabetes. In these patients, it may be more difficult to adjust the dosage of insulin.

THYROTOXICOSIS. Beta blockade may mask certain clinical signs of hyperthyroidism. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

PRECAUTIONS. *General.* Propranolol should be used with caution in patients with impaired hepatic or renal function. INDERAL (propranolol HCl) is not indicated for the treatment of hypertensive emergencies.

Beta adrenoreceptor blockade can cause reduction of intraocular pressure. Patients should be told that INDERAL may interfere with the glaucoma screening test. Withdrawal may lead to a return of increased intraocular pressure.

Clinical Laboratory Tests. Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

DRUG INTERACTIONS. Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if INDERAL is administered. The added catecholamine-blocking action may produce an excessive reduction of resting sympathetic nervous activity which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility. Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In 18-month studies in both rats and mice, employing doses up to 150 mg/kg/day, there was no evidence of significant drug-induced toxicity. There were no drug-related tumorigenic effects at any of the dosage levels. Reproductive studies in animals did not show any impairment of fertility that was attributable to the drug.

Pregnancy. Pregnancy Category C. INDERAL has been shown to be embryotoxic in animal studies at doses about 10 times greater than the maximum recommended human dose.

There are no adequate and well-controlled studies in pregnant women. INDERAL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. INDERAL is excreted in human milk. Caution should be exercised when INDERAL is administered to a nursing woman.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS. Most adverse effects have been mild and transient and have rarely required the withdrawal of therapy.

Cardiovascular. bradycardia; congestive heart failure, intensification of AV block, hypotension, paresthesia of hands, thrombocytopenic purpura, arterial insufficiency, usually of the Raynaud type.

Central Nervous System. lightheadedness; mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia, visual disturbances, hallucinations; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Gastrointestinal. nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis.

Allergic. pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Respiratory. bronchospasm.

Hematologic. agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Auto-Immune. In extremely rare instances, systemic lupus erythematosus has been reported.

Miscellaneous. alopecia, LE-like reactions, psoriasiform rashes, dry eyes, male impotence, and Peyronie's disease have been reported rarely. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been associated with propranolol.

DOSAGE AND ADMINISTRATION. INDERAL LA provides propranolol hydrochloride in a sustained-release capsule for administration once daily. If patients are switched from INDERAL tablets to INDERAL LA capsules, care should be taken to assure that the desired therapeutic effect is maintained. INDERAL LA should not be considered a simple mg for mg substitute for INDERAL. INDERAL LA has different kinetics and produces lower blood levels. Retitration may be necessary especially to maintain effectiveness at the end of the 24-hour dosing interval.

HYPERTENSION—*Dosage must be individualized.* The usual initial dosage is 80 mg INDERAL LA once daily, whether used alone or added to a diuretic. The dosage may be increased to 120 mg once daily or higher until adequate blood pressure control is achieved. The usual maintenance dosage is 120 to 160 mg once daily. In some instances a dosage of 640 mg may be required. The time needed for full hypertensive response to a given dosage is variable and may range from a few days to several weeks.

ANGINA PECTORIS—*Dosage must be individualized.* Starting with 80 mg INDERAL LA once daily, dosage should be gradually increased at three to seven day intervals until optimum response is obtained. Although individual patients may respond at any dosage level, the average optimum dosage appears to be 160 mg once daily. In angina pectoris, the value and safety of dosage exceeding 320 mg per day have not been established.

If treatment is to be discontinued, reduce dosage gradually over a period of a few weeks (see WARNINGS).

MIGRAINE—*Dosage must be individualized.* The initial oral dose is 80 mg INDERAL LA once daily. The usual effective dose range is 160-240 mg once daily. The dosage may be increased gradually to achieve optimum migraine prophylaxis. If a satisfactory response is not obtained within four to six weeks after reaching the maximum dose, INDERAL LA therapy should be discontinued. It may be advisable to withdraw the drug gradually over a period of several weeks.

HYPERTROPHIC SUBAORTIC STENOSIS—80-160 mg INDERAL LA once daily.

PEDIATRIC DOSAGE—At this time the data on the use of the drug in this age group are too limited to permit adequate directions for use.

REFERENCES

1. Holland OB, Nixon JV, Kuhnert L: Diuretic-induced ventricular ectopic activity. *Am J Med* 1981;70:762-768. **2.** Holme I, Helgeland A, Hjermann I, et al: Treatment of mild hypertension with diuretics. The importance of ECG abnormalities in the Oslo study and in MRFIT. *JAMA* 1984;251:1298-1299.

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(Continued from Page 619)

Wednesday. Contact: American College of Cardiology, 9111 Old Georgetown Rd., Bethesda, MD 20814.

July 13-20—**Cardiovascular Med. & Surgery & Critical Care Medicine.** Stanford University at Mauna Kea Beach Hotel, Kamuela, Hawaii. Saturday-Saturday.

July 19-21—**Cardiovascular Fitness Sports Medicine and Nutrition.** Mercy Medical Center, Redding. Friday-Sunday. Fee: $100. Contact: Shelly Underwood, Mercy Medical Center, PO Box 6009, Redding 96099. (916) 243-2121.

July 19-21—**Coronary Artery Disease and Sudden Death: Primary and Secondary Prevention.** International Medical Education Corp. at Marriott Hotel, Newport Beach, CA. Friday-Sunday. 13 hours. Fee: $295. Contact: IMEC, 64 Inverness Dr. E., Englewood, CO 80112.

EMERGENCY MEDICINE

May 15-19—**Wound Management Workshop.** UCSD at Holiday Inn at the Embarcadero, San Diego. Monday-Friday. 19 hrs.

May 20-24—**Topics in Emergency Medicine.** UCSF at Sheraton at Fishermans Wharf, San Francisco. Monday-Friday. 33 hrs. Fee: $400.

June 7-9—**14th Annual Scientific Assembly.** American College of Emergency Physicians at Doubletree Inn, Monterey. Friday-Sunday. No Fee. Contact: Sheila M. Johnson, CAL/ACEP, 505 N. Sepulveda Blvd., Manhattan Beach, CA 90266. (213) 374-4039.

June 20-21—**6th Annual Trauma Seminar.** Charles R. Drew Postgraduate Medical School at Disneyland Hotel, Anaheim. Thursday-Friday. 16 hrs. Contact: Dr. S. Bala, (213) 603-4510.

June 24-28—**Postgraduate Institute for Emerg. Physicians, Symposium 111.** UCSD at Hanalei Hotel, San Diego. Monday-Friday. 13-36 hrs. Fee: $200-675.

June 27-30—**Update in Emergency Medicine.** Mercy Medical Center, Redding at Salmon River (Whitewater rafting trip). Thursday-Sunday. 10 hrs. Fee: $125. Contact: Shelly Underwood, Mercy Medical Center, Redding, PO Box 6009, Redding, CA 96099-6009. (916) 243-2121.

July 3-6—**Wilderness Emergency Care.** Mercy Medical Center, Redding. Wednesday-Saturday. 10 hrs. Fee: $125. Contact: Shelly Underwood, Mercy Medical Center, PO Box 6009, Redding, CA 96099. (916) 243-2121.

July 12-14—**Update in Emergency Medicine.** Mercy Medical Center, Redding. Friday-Sunday. 10 hrs. Fee: $100. Contact: Shelly Underwood, Mercy Medical Center, PO Box 6009, Redding, CA 96099. (916) 243-2121.

INTERNAL MEDICINE

May 17-18—**Clinical Concerns in Hemodialysis Therapy.** Rutgers Medical School at Sheraton Harbor Island West Hotel, San Diego. Friday-Saturday. 11.5 hrs. Contact: Richard A. Sherman, MD, Academic Health Science Center, UMDNJ-Rutgers Medical School, CN-19, New Brunswick, NJ 08903.

June 15-22—**7th Annual Liver Biopsy Workshop.** Liver Research and Educational Foundation and USC at Mauna Kea Beach Hotel, Hawaii. Saturday-Saturday. 28 hrs. Contact: Jerry McDaniel Travel Management, (213) 658-7777.

June 19-21—**Gastroenterology: Recent Developments in Theory and Practice.** UCSF at Mark Hopkins Hotel, San Francisco. Wednesday-Friday. Fees: $375.

June 21-23—**California Society of Internal Medicine—Annual Meeting** at Hotel Del Coronado, Coronado. Friday-Sunday. 3 hrs. Contact: Carol Holland Parlette, CSIM, 703 Market Street, San Francisco 94103.

June 24-28—**Advances in Internal Medicine.** UCSF at Hotel Meridien, San Francisco. Fee: $420.

OPHTHALMOLOGY

May 18—**Neodymium—YAG Laser Course.** Jules Stein Eye Institute at Los Angeles. Saturday. 8 hrs. Fee: $200. Contact: Lu Hendricks, JSEI, 800 Westwood Plaza, Los Angeles 90024. (213) 825-4617.

June 6-8—**Cosmetic Blepharoplasty Workshop.** Jules Stein Eye Institute at Los Angeles. Thursday-Saturday. 18 hrs. Fee: $750. Contact: Lu Hendrcks, JSEI, 800 Westwood Plaza, Los Angeles 90024. (213) 825-4617.

June 29-July 3—**Pacific Coast Oto-Ophthalmological Society Annual Meeting** at Hotel Del Coronado, Coronado. Saturday-Wednesday. Contact: Rober-Christensen, MD, UCLA Med Center, 800 Westwood Plaza, Los Angeles, CA 90024.

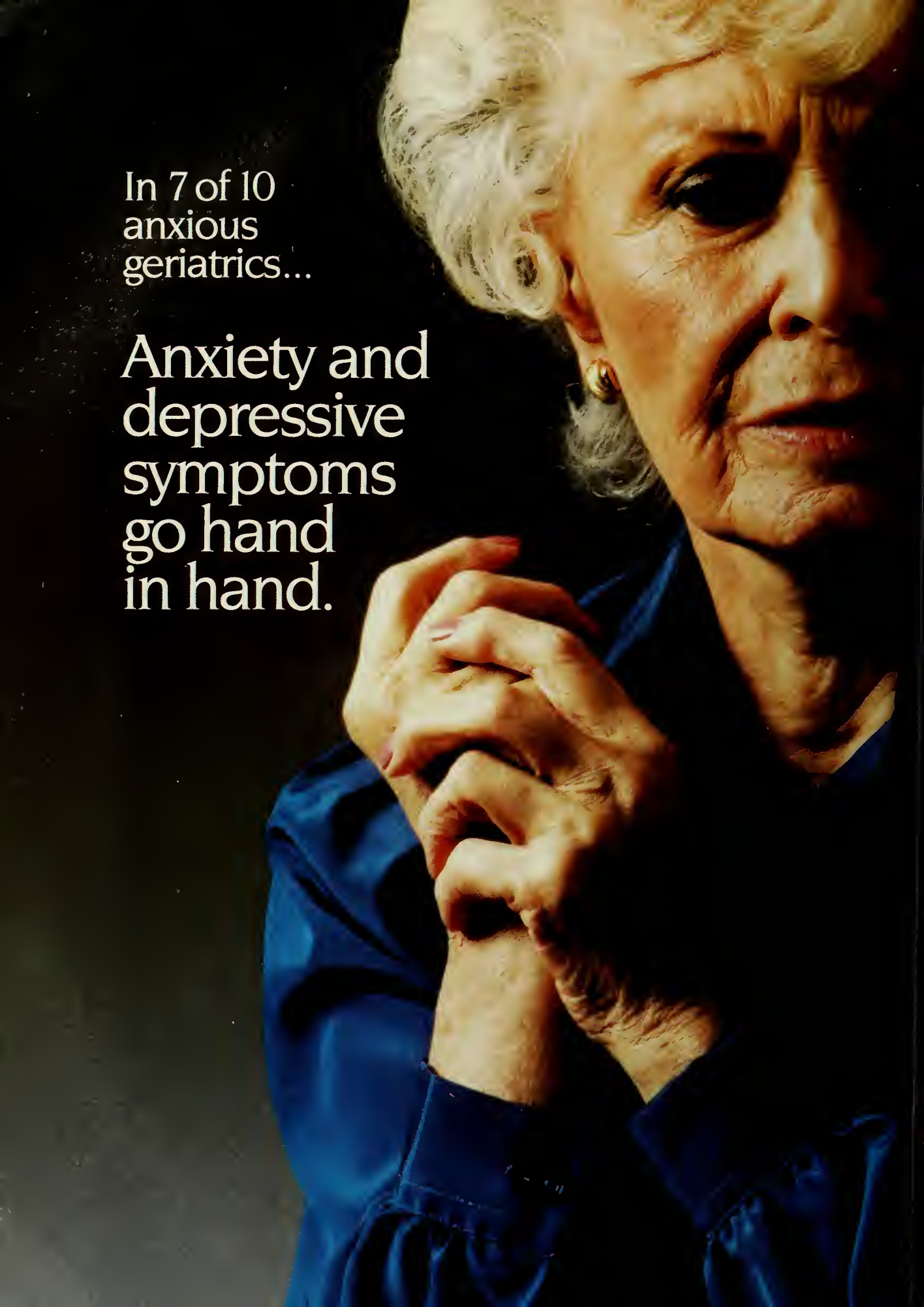
PATHOLOGY

May 23-24—**Symposium on Current Issues in Anatomic Pathology.** UCSF. Thursday-Friday.

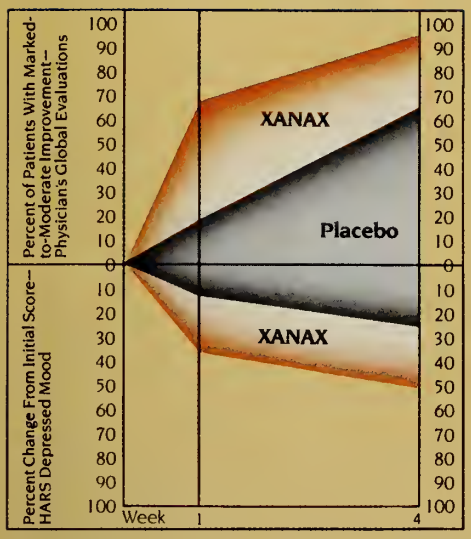
PEDIATRICS

May 15—**Los Angeles Pediatric Society—Annual Spring Meeting** at Los Angeles. Wednesday. Con-

(Continued on Page 626)


In 7 of 10
anxious
geriatrics...
Anxiety and
depressive
symptoms
go hand
in hand.

Xanax rapidly relieves anxiety with depressive symptoms.


Percent of Patients With Marked-to-Moderate Improvement—Physician's Global Evaluations
Percent Change From Initial Score—HARS Depressed Mood
100 90 80 70 60 50 40 30 20 10 0
XANAX
Placebo
XANAX
Week 1 4

In a recent clinical study[1] of 83 geriatric patients with clinical anxiety, 73% were diagnosed as having symptoms of depressed mood.

XANAX is well suited for therapy because it demonstrates greater efficacy than placebo in reducing the Hamilton Anxiety Rating Scale Total Score and individual items including depressed mood (see Figure).

With clinical advantages for geriatric patients.

- **Rapidly relieves** the symptoms of anxiety
- **Rapidly relieves** associated depressed mood
- **Well tolerated**—mild, transient drowsiness, the most commonly reported side effect the first week of therapy, shows a marked decrease thereafter and is not significantly different from that of placebo
- **Does not cause** cardiotoxicity
- **Specific geriatric dosage**—0.25 mg, two or three times daily

1 Cohn JB. Double-blind safety and efficacy comparison of alprazolam and placebo in the treatment of anxiety in geriatric patients. *Curr Ther Res* 1984;35(1):100-112.

Xanax® 0.25 mg Tablets
alprazolam C IV

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Kalamazoo, Michigan 49001 USA

Please see next page for brief summary of prescribing information.

XANAX® Tablets
(alprazolam) ℞

CONTRAINDICATIONS
Patients with sensitivity to this drug or other benzodiazepines and in acute narrow angle glaucoma

WARNINGS
Not of value in psychotic patients. Caution patients against hazardous occupations requiring complete mental alertness and about the simultaneous ingestion of alcohol and other CNS depressant drugs.

Benzodiazepines can cause fetal harm in pregnant women. Warn patients of the potential hazard to the fetus. Avoid during the first trimester.

PRECAUTIONS
General: The dosage of XANAX Tablets should be reduced or withdrawn gradually, since withdrawal seizures have been reported upon abrupt withdrawal. If XANAX is combined with other psychotropics or anticonvulsant drugs, consider drug potentiation. (See Drug Interaction section.) Exercise the usual precautions regarding size of the prescription for depressed or suicidal patients. In elderly and debilitated patients, use the lowest possible dosage. (See Dosage and Administration.) Observe the usual precautions in treating patients with impaired renal or hepatic function.

Information for Patients: Alert patients about: (a) consumption of alcohol and drugs, (b) possible fetal abnormalities, (c) operating machinery or driving, (d) not increasing dose of the drug due to risk of dependence, (e) not stopping the drug abruptly. *Laboratory Tests:* Not ordinarily required in otherwise healthy patients. *Drug Interactions:* Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistamines, ethanol and other CNS depressants. Pharmacokinetic interactions with benzodiazepines have been reported. *Drug/Laboratory Test Interactions:* No consistent pattern for a specific drug or specific test. *Carcinogenesis, Mutagenesis, Impairment of Fertility:* No carcinogenic potential or impairment of fertility in rats. *Pregnancy.* See Warnings. *Nonteratogenic Effects:* The child born of a mother on benzodiazepines may be at some risk for withdrawal symptoms and neonatal flaccidity. *Labor and Delivery.* No established use. *Nursing Mothers:* Benzodiazepines are excreted in human milk. Women on XANAX should not nurse. *Pediatric Use:* Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS
Side effects are generally observed at the beginning of therapy and usually disappear with continued medication. In the usual patient, the most frequent side effects are likely to be an extension of the pharmacological activity of XANAX, e.g., drowsiness or lightheadedness.

Central nervous system: Drowsiness, lightheadedness, depression, headache, confusion, insomnia, nervousness, syncope, dizziness, akathisia, and tiredness/sleepiness.

Gastrointestinal: Dry mouth, constipation, diarrhea, nausea/vomiting, and increased salivation.

Cardiovascular: Tachycardia/palpitations, and hypotension.

Sensory: Blurred vision.

Musculoskeletal: Rigidity and tremor.

Cutaneous: Dermatitis/allergy.

Other side effects: Nasal congestion, weight gain, and weight loss.

In addition, the following adverse events have been reported with the use of anxiolytic benzodiazepines: dystonia, irritability, concentration difficulties, anorexia, loss of coordination, fatigue, sedation, slurred speech, jaundice, musculoskeletal weakness, pruritus, diplopia, dysarthria, changes in libido, menstrual irregularities, incontinence and urinary retention.

Paradoxical reactions such as stimulation, agitation, increased muscle spasticity, sleep disturbances, and hallucinations may occur. Should these occur, discontinue the drug.

During prolonged treatment, periodic blood counts, urinalysis, and blood chemistry analysis are advisable. Minor EEG changes, of unknown significance, have been observed.

DRUG ABUSE AND DEPENDENCE
Physical and Psychological Dependence: Withdrawal symptoms have occurred following abrupt discontinuance of benzodiazepines. Withdrawal seizures have occurred upon rapid decrease or abrupt discontinuation of therapy. In all patients, dosage should be gradually tapered under close supervision. Patients with a history of seizures or epilepsy should not be abruptly withdrawn from XANAX. Addiction-prone individuals should be under careful surveillance. *Controlled Substance Class:* XANAX is a controlled substance and has been assigned to schedule IV.

DOSAGE AND ADMINISTRATION
The usual starting dose is 0.25 to 0.5 mg. t.i.d. Maximum total daily dose is 4 mg. In the elderly or debilitated, the usual starting dose is 0.25 mg, two or three times daily. Reduce dosage gradually when terminating therapy, by no more than one milligram every three days.

CAUTION: FEDERAL LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION. B-3-S

Upjohn THE UPJOHN COMPANY
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CONTINUING MEDICAL EDUCATION

(Continued from Page 623)

tact: Eve Black, Exec. Sec., PO Box 2022, Inglewood 90305. (213) 757-1198.

May 25-27—**Annual Spring Meeting, N. Calif. Chapter, American Academy of Pediatrics.** American Academy of Pediatrics at Hyatt Regency, Monterey. Saturday-Monday. 11 hrs. Contact: Am. Academy of Ped., (415) 459-4775. Fee: $125-$225.

May 30-June 1—**Pediatric Rehabilitation Program.** UCD at Doubletree Inn, Monterey. Thursday-Saturday.

June 21-22—**Pediatric Pulmonary Update—1985.** Children's Hospital and Health Center at San Diego Hilton Beach and Tennis Resort. Friday-Saturdy. Contact: Sung Min Park, MD, Children's Hospital and Health Center, 8001 Frost Street, San Diego 92123. (619) 576-5854.

June 22-29—**3rd National Kaiser Permanente Pediatrics Conference** at Maui, Hawaii. One Week. 22.5 hrs. Fee: $100. Contact: Steven Black, MD (45) 428-5815.

July 5-7—**Pediatrics for the Practitioner.** American Academy of Pediatrics at Anaheim. Friday-Sunday. 13 hrs. Fee: $225. Contact: Eve Black, PO Box 2134, Inglewood, CA 90305.

PSYCHIATRY

June 7—**9th Annual Psychiatric Symposium.** Southern California Permanente Medical Group at Anaheim Marriott Hotel. Sunday. Contact: Lilia M. Guerrero, So. CA. Kaiser Permanente Medical Care Program, 4747 Sunset Blvd., Los Angeles, CA 90027. (213) 667-4241.

RADIOLOGY

May 17-19—**10th Annual Spring Diagnostic Ultrasound Conference.** Los Angeles Radiological Society at Century Plaza Hotel, Los Angeles. Friday-Sunday. 17 hrs. Contact: Zbigniew Petrovich, MD, c/o L.A. Radiological Society, PO Box 91215, Los Angeles 90009-1215. (213) 642-0921.

May 19-25—**5th Annual Post Conference Seminar.** Los Angeles Radiological Society at Turtle Bay Hilton and Country Club, Kahuku, Oahu. Sunday-Saturday. 18 hrs. Contact: Zbigneiw Petrovich, MD, c/o Los Angeles Radiological Society, PO Box 91215, Los Angeles 90009-1215. (213) 642-0921.

June 9-12—**Advanced Echo-Doppler: 1985 and Complementary Imagina Tech.,** ACC at Sheraton Harbor Island, San Diego. Sunday-Wednesday. Contact: CC, 9111 Old Georgetown Rd., Bethesda, MD., 20814. (301) 897-5400.

SURGERY

May 30-31—**14th Annual Neurosurgery and 8th Annual Neurosurgical Nurses Conference.** UCSF at

(Continued on Page 631)

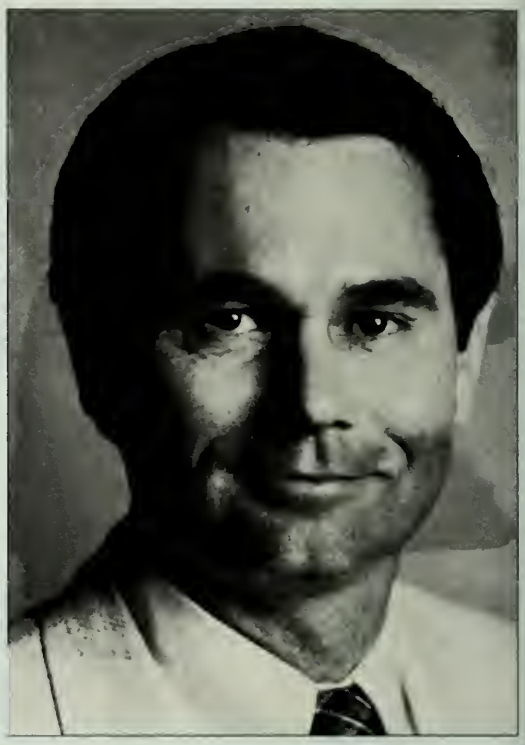
IDAHO MEDICAL ASSOCIATION

93rd Annual Meeting

July 24-27, 1985 • Sun Valley, Idaho

An Invitation to Sun Valley

July 24-27, 1985



We are pleased to extend to you a cordial invitation to attend the 93rd Annual Meeting of the Idaho Medical Association in the beautiful setting of Idaho's Sun Valley. An excellent scientific session has been planned that should appeal to all types of physicians, family practitioners and specialists alike. It should be a good opportunity not only to enjoy beautiful Sun Valley, but also receive 11 credit hours of Category I at an informative scientific session.

John W. Gerwels, MD
President, Idaho Medical Association

IDAHO MEDICAL ASSOCIATION

93rd Annual Meeting

Sun Valley • July 24-27, 1985

Sun Valley Registration Form

Name _____

Address _____

City _____ State _____ Zip _____

Will Arrive _____, 1985 at _____ &

Depart _____, 1985 at _____

Confirmed reservations require an advance deposit equal to one night's room rental.

PLEASE RETURN FORM WITH DEPOSIT TO:
Sun Valley Reservation Office
Sun Valley, Idaho 83353

Questions: Call Sun Valley Toll-free reservations number (800) 635-8261.
Please mention IMA meeting when calling Sun Valley.

Please Check Accommodations Desired (European Plan)

Hotel Rooms: Sun Valley Lodge or Inn
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☐ Studio, $78 per day
☐ One-Bedroom, $98 to $120 per day
☐ Two-Bedroom, $130 to $180 per day
☐ Three-Bedroom, $155 to $230 per day

Each additional person $10

Deadline for Reservations: June 24, 1985
Cancellations: No deposit refunds on cancellations received less than 7 days prior to arrival. There is a $10 per person processing charge on all cancellations.

IDAHO MEDICAL ASSOCIATION

93rd Annual Meeting

Sun Valley, Idaho • July 24-27, 1985

9 a.m.-5 p.m. **House of Delegates**

THURSDAY, JULY 25

7:45 a.m. **Welcome**
John W. Gerwels, MD, President, IMA

8:00 a.m. **Update on Pathophysiology of Peptic Ulcer Disease**
Keith G. Tolman, MD

9:00 a.m. **Dysphagia: A Common Clinical Problem**
Jorge E. Valenzuela, MD

10:30 a.m. **Evaluation and Surgical Management**
Thomas R. DeMeester, MD

11:30 a.m. **Disorders of Gastric Emptying**
Jorge E. Valenzuela, MD

2:00 p.m. **Implications of Hepatitis B in Health Care Workers**
Keith G. Tolman, MD

3:00 p.m. **Preoperative Evaluation of Patients with Gastro-Esophageal Reflux**
Tom R. DeMeester, MD

4:00 p.m. **Panel Discussion:**
Medical vs Surgical Management of Esophageal Reflux and What Is the Procedure of Choice
Medical vs Surgical Management of Peptic Ulcer Disease and What Is the Procedure of Choice
Thomas R. DeMeester, MD, Keith G. Tolman, MD, and Jorge E. Valenzuela, MD

FRIDAY, JULY 26

7:45 a.m. **Introduction**
Kenneth L. Judy, MD, *Chairman, IMA Program Commit*

8:00 a.m. **Implications of DRGs in Care of the Cancer Patien**
Albert M. Brady, MD

9:00 a.m. **Thyroid Nodules: A Practical Approach to Management**
Kenneth E. W. Melvin, MD

10:30 a.m. **Pain Control: With Emphasis on Terminal Disease**
Albert M. Brady, MD

11:30 a.m. **Estrogens and Osteoporosis**
Kenneth E. W. Melvin, MD

SATURDAY, JULY 27

8:30 a.m. **Closing Session, House of Delegates**

Jorge E. Valenzuela, MD
Chief, Section of Gastroenterology, LAC-USC Medical Center, Los Angeles

Albert M. Brady, MD
Medical Oncologist in Private Practice, Portland

Tom Ryan DeMeester, MD
Professor of Thoracic and Cardiovascular Surgery, Creighton University School of Medicine, Omaha

Keith G. Tolman, MD
Associate Professor of Medicine, University of Utah College of Medicine, Salt Lake City

Kenneth E. W. Melvin, MD
St. Vincent's Hospital, Portland

Registration Fee: $150 for non-IMA Members and out-of-state physicians.

For Information Contact: Idaho Medical Association, PO Box 2668, Boise, ID 83701; Telephone: (208) 344-7888

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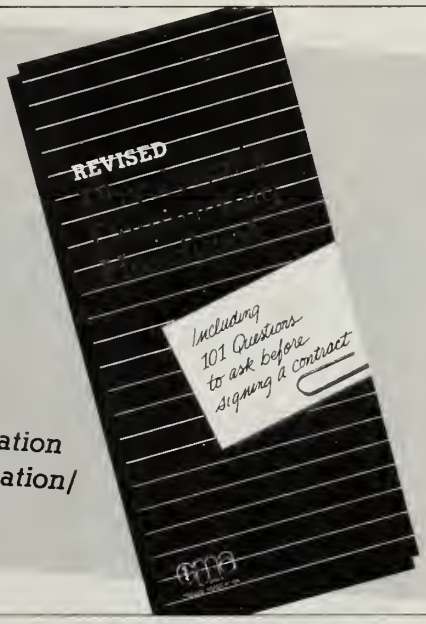
Revised
PHYSICIAN'S CONTRACTING HANDBOOK

prepared by
the California Medical Association
Department of Contract Evaluation/
Negotiation Services



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San Francisco, CA 94103-1233

CONTINUING MEDICAL EDUCATION

(Continued from Page 626)

San Francisco Hilton Hotel, San Francisco. Thursday-Friday. 15.5 hrs.

June 1—**General Surgery.** UCSF at Fresno. Saturday.

June 7-8—**Southwestern Regional Flap Workshop.** UCLA. Friday-Saturday. Contact: Daniel E. Gormley, MD, 412 W. Carroll, Ste. 207, Glendora, CA 1740.

June 7-8—**Prothetics/Orthotics.** UC, Davis at Beverly Garland Hotel, Sacramento. Friday-Saturday.

June 15-20—**Fingers to the Toes.** UC, Davis at Stanford Sierra Camp, Fallen Leaf Leak, CA. Saturday-Thursday.

June 17-21—**Basic Microsurgery Training Workshop.** UCSD at San Diego. Monday-Friday. 34 hrs. Fee: $1,200.

June 17-21—**Symposium on the Temporamandibular Joint.** UCSF at Maui Marriott Hotel, Maui, Hawaii. Monday-Friday. Fee: $425.

June 19-22—**Superficial Anatomy and Cutaneous Surgery.** UC, San Diego. Wednesday-Saturday. Fee: $250-$600.

OF INTEREST TO ALL PHYSICIANS

May 18—**Management of Rehabilitation in 3rd Stage Stroke.** National Stroke Association at Stroke Activities Center, Palm Springs. Saturday. 4 hrs. Contact: Diane Hanner, 1776 N. Palm Canyon, Palm Springs, CA 92262. (619) 323-7670.

May 21-24—**6th Annual Verne T. Inman Lectureship and 20th Annual Scientific Program.** UCSF at San Francisco. Tuesday-Friday. 14 hrs.

May 19-23—**Current Concepts in Primary Care: 12th Annual Family Practice Refresher Course.** UCD at Napa Valley. Sunday-Thursday.

May 30—**New in Vitro Assays for Allergen Specific IgE and IgG 4 Antibodies.** UCD at Hilton Hotel, Los Angeles. Thursday. Contact: Georges M. Halpern, MD, Division of Rheumatology/Allergy, UCD.

June 5-9—**28th Annual Clinical Conference and 3rd Annual Training Institute.** Northern California Pyschotherapy Society at Asilomar, Pacific Grove.

(Continued on Page 724)

Before prescribing, see complete prescribing information in SK&F CO. literature or *PDR*. The following is a brief summary.

* WARNING

This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Contraindications: Concomitant use with other potassium-sparing agents such as spironolactone or amiloride. Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: Do **not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired.** If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics.

Precautions: The bioavailability of the hydrochlorothiazide component of 'Dyazide' is about 50% of the bioavailability of the single entity. Theoretically, a patient transferred from the single entities of Dyrenium (triamterene, SK&F CO.) and hydrochlorothiazide may show an increase in blood pressure or fluid retention. Similarly, it is also possible that the lesser hydrochlorothiazide bioavailability could lead to increased serum potassium levels. However, extensive clinical experience with 'Dyazide' suggests that these conditions have not been commonly observed in clinical practice. Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids, and during concurrent use with amphotericin B or corticosteroids or corticotropin [ACTH]). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Cumulative effects of the drug may develop in patients with impaired renal function. Thiazides should be used with caution in patients with impaired hepatic function. They can precipitate coma in patients with severe liver disease. Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic and hemolytic anemia have been reported with thiazides. Thiazides may cause manifestation of latent diabetes mellitus. The effects of oral anticoagulants may be decreased when used concurrently with hydrochlorothiazide; dosage adjustments may be necessary. Clinically insignificant reductions in arterial responsiveness to norepinephrine have been reported. Thiazides have also been shown to increase the paralyzing effect of nondepolarizing muscle relaxants such as tubocurarine. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. Triamterene has been found in renal stones in association with the other usual calculus components. Therefore, 'Dyazide' should be used with caution in patients with histories of stone formation. A few occurrences of acute renal failure have been reported in patients on 'Dyazide' when treated with indomethacin. Therefore, caution is advised in administering nonsteroidal anti-inflammatory agents with 'Dyazide'. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine. Hypokalemia is uncommon with 'Dyazide', but should it develop, corrective measures should be taken such as potassium supplementation or increased dietary intake of potassium-rich foods. Corrective measures should be instituted cautiously and serum potassium levels determined. Discontinue corrective measures and 'Dyazide' should laboratory values reveal elevated serum potassium. Chloride deficit may occur as well as dilutional hyponatremia. Concurrent use with chlorpropamide may increase the risk of severe hyponatremia. Serum PBI levels may decrease without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. 'Dyazide' should be withdrawn before conducting tests for parathyroid function.

Thiazides may add to or potentiate the action of other antihypertensive drugs.

Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances; postural hypotension (may be aggravated by alcohol, barbiturates, or narcotics). Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and respiratory distress including pneumonitis and pulmonary edema, transient blurred vision, sialadenitis, and vertigo have occurred with thiazides alone. Triamterene has been found in renal stones in association with other usual calculus components. Rare incidents of acute interstitial nephritis have been reported. Impotence has been reported in a few patients on 'Dyazide', although a causal relationship has not been established.

Supplied: 'Dyazide' is supplied as a red and white capsule, in bottles of 1000 capsules; Single Unit Packages (unit-dose) of 100 (intended for institutional use only); in Patient-Pak™ unit-of-use bottles of 100.

BRS-DZ:L39

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DYAZIDE®

25 mg Hydrochlorothiazide/**50 mg** Triamterene/SKF

For the Majority of Patient Types

Over 50 ▪ Black ▪ Physically Active ▪ Asthmatic

*Not for initial therapy. See brief summary.

Serum K^+ and BUN should be checked periodically (see Warnings and Precautions).

Clinical Investigation

The Predictive Value of Physical Examinations for Ascites

STEVEN CUMMINGS, MD; MAXINE PAPADAKIS, MD; JANE MELNICK, MD;
GRETCHEN A. W. GOODING, MD, *and* LAWRENCE M. TIERNEY, Jr, MD, *San Francisco*

To determine the predictive value of physical signs for ascites, we compared the results of physical examination with those of abdominal sonography in 90 men in hospital with liver disease. The positive predictive values of shifting dullness and prominent fluid waves were low (51% and 73%). We divided the patients into two groups: those with prolonged prothrombin times (72% prevalence of ascites by sonogram), and those with normal prothrombin times (15% prevalence). In patients with prolonged prothrombin times, a prominent fluid wave had a very high positive predictive value for ascites (96%). Many patients with prolonged prothrombin times had ascites despite negative physical signs. In contrast, in those with normal prothrombin times, both shifting dullness and prominent fluid waves were usually falsely positive. Patients with normal prothrombin times and no shifting dullness rarely (2%) had ascites.

The predictive value of physical signs for ascites depends on the prevalence of ascites in groups of patients that are examined. The prothrombin time is a useful index for identifying inpatients with a high or low prevalence of ascites and the predictive value of physical signs is enhanced by interpreting them in combination with a patient's prothrombin time.

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The predictive value of diagnostic tests for a specific disorder depends on the prevalence of that disorder in the patients who undergo the test. This principle has been applied to a variety of laboratory tests but has not been widely applied to the physical examination.[1] According to this principle, in patients who have a low prevalence of the disorder, positive diagnostic physical findings are more likely to be "false positives" than findings in patients who have a higher prevalence of the disorder. The predictive value of diagnostic tests can be improved by identifying subsets of patients who have a high or low prevalence of the disorder. This concept has been very fruitfully applied, for example, to interpretation of exercise testing for coronary artery disease.[2] We believe that a similar strategy might improve the interpretation of some aspects of physical examinations.

Many physicians regard physical findings for ascites as unreliable. Therefore, we undertook this study to determine the predictive value of commonly used physical signs for ascites and to determine whether dividing patients into subgroups with a high or low prevalence of ascites could improve the interpretation of these physical signs.

Ascites is an important finding in patients with liver disease. The presence of ascites predicts cirrhosis in patients who have chronic active hepatitis,[4] has prognostic significance in patients who have chronic liver disease[5] and is an important factor in determining the risk of surgical procedures in patients with liver disease.[6] Because spontaneous bacterial peritonitis is also liable to develop in patients with ascites, physical findings of ascites often lead to urgent diagnostic paracentesis in febrile patients.

Until the advent of abdominal ultrasonography, ascites was diagnosed primarily by physical examination and abdominal paracentesis. Physical examination is an immediate and inexpensive way to detect ascites, but the predictive value of individual physical findings is uncertain. One study has reported that classic physical findings had relatively low predic-

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tive values for ascites in a small group of patients.[3] Although the accuracy of abdominal sonography in detecting ascites has not been thoroughly investigated, some studies have suggested that sonograms are very sensitive and specific for ascites. Static sonograms detect as little as 100 ml of ascitic fluid[7] and, especially when real-time examinations are used, false-positive sonograms for ascites appear to be uncommon.[8] However, abdominal sonograms are not always immediately available and they are relatively expensive; the charge is customarily between $120 and $200.

Therefore, to determine the predictive value of common physical signs for ascites, we prospectively compared common physical signs with the findings from abdominal sonograms in men in hospital with liver disease. To determine the effect of the prevalence of ascites on the predictive value of the physical findings we divided the patients into two groups: one group with prolonged prothrombin times who had a very high prevalence of ascites and a second group with normal prothrombin times who had a much lower prevalence of ascites.

Patients and Methods

We recruited patients for the study from the Inpatient Medical Service of San Francisco Veterans Administration Hospital. To identify all eligible patients, we systematically contacted house officers on the day after they received admissions and at the morning reports and periodically surveyed charts of patients on the medical service. Patients were included in the study if they had any *two* of the following signs of liver disease: (1) elevated serum alkaline phosphatase concentration, (2) elevated direct serum bilirubin value, (3) elevated serum aspartate amino transferase or alanine amino transferase level, (4) liver span greater than 12 cm by examination. Suspicion that ascites was present was *not* a criterion for inclusion in or exclusion from the study. Patients were excluded if they had had an abdominal surgical procedure within the previous month, or were unable or unwilling to undergo either physical examination or abdominal sonography. Enrollment was continued until each examiner had completed 60 examinations.

Each of the patients was examined by two examiners for four signs of ascites: shifting dullness, fluid waves, bulging flanks and abdominal distention. Three examiners participated in the study, all board-certified internists: a fellow in general internal medicine, a chief resident in medicine and the assistant chief of the medical service. The examiners were unaware of each other's findings, the results of a patient's abdominal sonogram and a patient's prothrombin time. All physical examinations were done within 72 hours of the sonogram.

Shifting dullness was sought by percussing the patient's right flank with the patient first lying flat and then lying in the right lateral decubitus position supported by a 45-degree-angle foam pillow. Shifting dullness was deemed present if the levels at which dullness was detected differed by at least 1 cm. Fluid waves were sought by sharply tapping each flank while an assistant pressed the edge of his hand longitudinally into the abdomen. The examiners rated fluid waves as absent, slight or prominent. However, they often disagreed about the presence of "slight" fluid waves. When one examiner rated a fluid wave as "slight," the other rated it as "absent" in 61% of instances. Therefore, for the analysis, ratings of slight and absent were combined, and fluid waves were considered present only if rated as "prominent."

Before the study began, the three examiners evaluated several nonstudy subjects for the physical signs of ascites to standardize their methods and judgments. A fourth investigator observed each examiner's technique at the beginning and the end of the study. This investigator detected no difference among the examiners in techniques and no changes in techniques over the course of study.

Each patient underwent both static and real-time abdominal sonography. Each subject was scanned supine in the parasagittal and the transverse planes. If ascites was present, the amount was rated on a scale from slight (1+) to massive (4+). The sonograms were read by a staff radiologist who was unaware of the results of the physical examinations.

Each patient's current prothrombin time and the presumed cause of his liver disease was recorded from the medical record by the investigator who did not participate in either the physical examinations or interpretation of the sonograms. We hypothesized that a prolonged prothrombin time, a marker of advanced hepatocellular dysfunction,[9] would be associated with a higher prevalence of ascites. Prothrombin times were determined by the Quick method using a Simplastin reagent. Normal upper limit for the laboratory during the period of the study was 12 seconds; therefore, we defined a prothrombin time as abnormal if it exceeded 12 seconds.

We analyzed the data from each examiner separately and then, to determine overall sensitivity, specificity and predictive value of signs, we pooled data from all examinations for each sign. We used standard definitions of sensitivity, specificity and predictive value[1]: sensitivity defined as the proportion of patients with ascites by sonogram who had a positive sign, specificity as the proportion without ascites who had a negative sign, and positive predictive value as the proportion with a positive sign who had ascites. We calculated confidence intervals for proportions, and we used McNemar's test to determine whether there were significant differences between individual examiners in the sensitivity or specificity of their physical examinations. We also carried out multiple logistic regression analyses to determine whether the addition of other physical signs would further improve the predictive value of the physical examination.

This study was approved by the Committee on Human Experimentation at the University of California, San Francisco.

Results

Ninety men with liver disease underwent two physical examinations and abdominal ultrasonography. Their liver disease was most often attributed to excessive consumption of alcohol (Table 1). Thirty patients (33%) had ascites shown by abdominal sonography. The ascites was rated as massive (4+) in 3, mild (2+) or moderate (3+) in 20 and slight (1+) in 7 patients.

The most sensitive sign for ascites was shifting dullness and the most specific was a prominent fluid wave (Table 2). Both examiners agreed about the presence or absence of shifting dullness in 78%, prominent fluid waves in 76%, bulging flanks in 79% and abdominal distention in 86% of the examinations. There were no significant differences in the

sensitivities and specificities of any of the physical signs between individual examiners ($P > .2$ for all pairs of examiners by McNemar's test).

Predictive Values of Physical Signs

Overall, the predictive values of physical signs were low. The positive predictive value of shifting dullness for ascites was 51% and for a prominent fluid wave was 73% (Table 2). All three examiners had very similar positive predictive values for shifting dullness (55%, 52%, 50%) and a prominent fluid wave (74%, 67%, 75%). The combination of shifting dullness and a prominent fluid wave had a 77% predictive value for ascites which was not significantly different from the predictive value of a fluid wave alone.

These physical findings were almost always positive when amount of ascites was massive or moderate; shifting dullness was present in 100% and prominent fluid waves in 89%. But physical signs were usually absent when the amount of ascites was slight; shifting dullness was present in 43% and fluid waves in 21%. Of the seven patients with slight amounts of ascites, six had prolonged prothrombin times.

Prothrombin Times, Prevalence of Ascites and Predictive Values of Physical Signs

To determine the effect of the prevalence of ascites on the predictive values of shifting dullness and prominent fluid waves we divided the patients into two groups: 31 patients with prolonged prothrombin times and 59 patients with normal prothrombin times. Two of the patients who had prolonged prothrombin times were receiving coumadin and were excluded from further analysis. Of the remaining 29 patients with prolonged prothrombin times, 21 (72%) had ascites. Of the 59 patients with normal prothrombin times, 9 (15%) had ascites.

Positive physical signs were generally correct in predicting ascites in patients with prolonged prothrombin times. However, in patients with normal prothrombin times, positive signs were usually false-positives (Figure 1). For example, the predictive value of a prominent fluid wave was 96% in patients with prolonged prothrombin times, but only 48% in patients with normal prothrombin times.

Negative physical signs were generally accurate in predicting the absence of ascites in patients with normal prothrombin times. For example, when no shifting dullness was detected in patients with normal prothrombin times, ascites was rarely (2%) present (Figure 1). However, in patients with prolonged prothrombin times, negative signs were often falsely negative. When no shifting dullness was detected in patients with prolonged prothrombin times ascites was present, nevertheless, in 43%.

The combination of a prominent fluid wave and a prolonged prothrombin time had the highest predictive value for ascites (96%). The combination of the absence of shifting dullness and a normal prothrombin time virtually excluded ascites. No other combinations of findings had better predictive values.

Discussion

We found that the predictive value of common physical signs for ascites was low in a group of 90 men in hospital with liver disease, who had a 33% prevalence of ascites as detected by ultrasonography. The predictive values we found are similar to those reported by Cattau and co-workers[3] for a small group of inpatients who had a 28% prevalence of ascites.

However, our study also shows that the interpretation of these physical signs for ascites depends on the prevalence of ascites in the type of patient examined. We found that the subgroup of patients with a prolonged prothrombin time had a high (72%) prevalence of ascites. In these patients, positive physical findings almost always correctly identified the presence of ascites. In particular, the presence of a prominent fluid wave in a patient with a prolonged prothrombin time had a very high (96%) predictive value for ascites.

TABLE 1.—*Presumed Cause of Liver Disease*

Alcohol	48
Congestive heart failure	7
Acute hepatitis	6
Malignant condition	6
Chronic hepatitis (viral or drug related)	6
Miscellaneous causes	3
Unknown or unspecified	14
Total	90

TABLE 2.—*Overall Sensitivity, Specificity and Positive Predictive Value of Physical Signs for Ascites**

Sign	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)
Shifting dullness	88	56	51
Prominent fluid wave	53	90	73
Abdominal distention	72	65	51
Bulging flanks	72	70	54

*Values represent proportion of pooled examination, n=180.

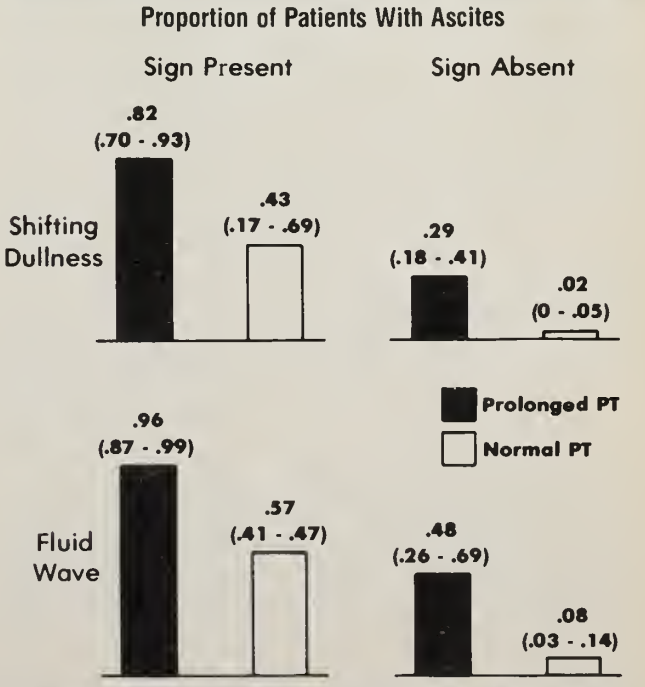

Figure 1.—Predictive value of physical signs for ascites in patients with normal and prolonged prothrombin times.

In the subgroup with a normal prothrombin time, negative physical signs quite accurately predicted the absence of ascites. In particular, the absence of shifting dullness and normal prothrombin time virtually excluded ascites (Figure 1).

Based on these findings, we believe that the combination of a carefully carried out physical examination and a prothrombin time can guide a more selective use of abdominal sonography. First, patients admitted to hospital who have liver disease, prolonged prothrombin times and a prominent fluid wave are very likely to have ascites and generally do not require sonography for confirmation. Second, patients who have liver disease but who have a normal prothrombin time and no shifting dullness are very unlikely to have ascites. Sonography to exclude ascites seldom will be necessary. Third, shifting dullness or prominent fluid waves in patients who have normal prothrombin times often will be falsely positive for ascites and abdominal sonography may be needed to settle the issue and should be done before paracentesis is attempted. Finally, many patients in hospital with liver disease and prolonged prothrombin times have ascites despite the absence of physical signs of ascites. Some clinical situations, such as unexplained fever, may warrant sonography to exclude ascites.

Since we studied a group of men in hospital with a high (33%) prevalence of ascites, our findings may not be completely applicable to other clinical settings. For example, the positive predictive values of these physical signs are likely to be lower in outpatient settings where ascites is less prevalent. The physical examinations were done in a standardized manner and examinations carried out less rigorously may be less accurate. We did not analyze the value of other biochemical tests in the diagnosis of ascites and it is possible that other tests may also serve to identify subgroups of patients with a high or low prevalence of ascites.

These findings illustrate how the predictive value of physical diagnostic signs, like that of other types of diagnostic tests, depends on the prevalence of the disorder being sought.[1] We believe that this principle can also be usefully applied to other physical diagnostic signs. The positive predictive value of physical signs will be higher when the disease is prevalent and lower when the disease is uncommon or unlikely.

We conclude that in unselected men in hospital with liver disease, physical signs of ascites, by themselves, are often misleading. Patients' prothrombin times are a useful index of the prevalence of ascites and the utility of physical signs for ascites can be substantially improved by interpreting these physical signs in combination with the patients' prothrombin times.

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Seizures and Death on a White River Float Trip

Report of Water Hemlock Poisoning

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White river rafting is becoming a major summer recreational activity throughout the United States. Many people who are ill prepared physically or emotionally to survive will find themselves isolated and in extremely dangerous situations without access to medical help. In addition to the physical dangers of drowning, there are dangers that exist in the concept of "living off the land" and foraging for food. Cicuta douglasii *is found in all of our western states, is extremely toxic and can easily be confused with wild parsnip or carrot. Physicians and poison control centers need to be aware of the common poisonous plants in their area and be prepared to treat cases of poisoning from these plants.*

(Landers D, Seppi K, Blauer W: Seizures and death on a white river float trip—Report of water hemlock poisoning. West J Med 1985 May; 142:637-640)

White river rafting is becoming a major recreational activity because of the large number of scenic rivers in the United States. A rough estimate of the number of people in Idaho involved in float trips annually would be in the range of 25,000 to 30,000. The Middle Fork of the Salmon River alone had about 8,000 people on it during 1980. Out of a total of 670 separate launches on this river, 373 of these were private launches in which no outfitter was present (Ken Olsen, Mackay Bar Idaho's Wilderness Company, oral communication, June 1984).

It is not a common practice for outfitters to allow consumption of any wild foliage while on the river with the exception of some berries, such as huckleberries and currant berries. However, since the publication of books by Euell Gibbons* that extolled the concepts of "returning to nature" and equating all things natural with being "good," many people are experimenting with living off the land and eating "edible" plants. *Cicuta douglasii,* the Western water hemlock plant, has roots that look like parsnip roots and have a parsnip or celerylike odor, thus tempting people to make the fatal mistake of eating them.[1] Unfortunately, there is a thin line between edible and poisonous plants, and when a mistake is made while on a rafting trip, the victims are usually far from any medical help and oftentimes inaccessible except by riverboat or helicopter.

In late April 1984, six out of eight men on a float trip on the Owyhee River in eastern Oregon were poisoned after eating what was thought to be wild parsnip. Four of the men each took from one to four small bites of the root (rhizome) while the other two men ate at least one of the rhizomes. About 45 minutes after eating the root, one person (case 1) had a grand mal seizure that the other men assumed was an epileptic seizure. When a second person (case 2) had a grand mal seizure about 15 minutes later, the remaining members of the party began to suspect that the roots they had eaten were poisonous. One of the four men who ate only a small amount of the root, a senior medical student at The University of Oregon Health Sciences Center, attempted to maintain the airways to protect the seizing patients; despite his efforts, however, the second man suffered cardiopulmonary arrest and could not be resuscitated.

The following case reports from the Southwest Idaho Poison Control Center at St Alphonsus Medical Center in Boise are presented to draw attention to a deadly poisoning that could occur in any of our western states.

Reports of Cases

Case 1

The patient, a 27-year-old man, was admitted to St Alphonsus Regional Medical Center in late April 1984, seven hours after ingesting a large rhizome of the water hemlock plant, *C douglasii (Cicuta vagans).* Seizure activity with generalized tonic-clonic movements had developed about 45 minutes after he ate the rhizome. The seizures lasted about two

**Stalking the Wild Asparagus* (1962), *Stalking the Healthful Herbs* (1966) and *Beachcomber's Handbook* (1967), all published by D. McKay Company, New York.

From the Emergency Department, St Alphonsus Regional Medical Center, and Southwest Idaho Poison Control Center (Dr Landers); the Southwest Idaho Family Practice Residency, Boise (Drs Seppi and Blauer), and the Department of Family Medicine, University of Washington School of Medicine, Seattle (Dr Landers). Dr Landers is now with the Department of Anesthesiology, University of Utah Medical Center, Salt Lake City.

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minutes each and occurred at 1345, 1415, 1440, 1517 and 1656 hours (Table 1). The patient had partial airway obstruction with cyanosis, bradycardia and decreased pulse pressure during the seizures; he did not suffer a respiratory arrest at any time. After the last seizure at 1656, the patient was quite lethargic but was arousable.

He was evacuated by helicopter to St Alphonsus where he had a workup and was treated. On examination he was lethargic but arousable and oriented to person and place but not to time. Blood pressure was 172/92 mm of mercury, the pulse rate 80 beats per minute and respirations 20 per minute. The skin was not cyanotic and showed no evidence of trauma.

TABLE 1.—*Seizure Sequence in Two Men Who Ingested Water Hemlock Rhizomes (Ingestion Occurred About 1300 hr)*

Seizure Episode	Time	
	Case 1	Case 2
1	1345	1400
2	1415	?
3	1440	1441
4	1517	1450*
5	...	1500*
6	1656	1535†

*A dreamlike state with low-volume yelling of nonintelligible sounds occurred between seizures 4 and 5.
†Cardiopulmonary arrest following seizure 6.

With the exception of the patient's lethargy, the physical examination showed no abnormalities.

After lavage of his stomach was done, he was given 60 grams of activated charcoal. An intravenous line was established for fluid replacement of lactated Ringer's solution and for venous access in case of the need for diazepam (Valium) for seizure control. During the patient's stay in the Emergency Department and hospital, no seizures were noted.

Laboratory studies on admission gave the following values: serum glucose, 199 mg per dl; creatinine, 1.8 mg per dl; uric acid, 15.6 mg per dl, and lactic dehydrogenase, 301 units. Serum electrolyte values were within normal range. Leukocytes numbered 17,400 per μl and the hemoglobin was recorded at 16.4 grams per dl.

A urinalysis showed 2+ occult blood with 0 to 2 leukocytes per high-power field and 0 to 2 erythrocytes per high-power field. A urine drug screen was negative.

An electroencephalogram that was done two days after ingestion of the water hemlock was diffusely abnormal. It showed synchronous and symmetrical bilateral theta activity of the type that might be seen with toxic metabolic conditions or increased intracranial pressure.

The patient was observed in hospital for two days, during which time he had no seizures and gradually became more arousable. Following dismissal from the hospital he continued to be amnestic for the seizure period and he had short

Figure 1.—*Cicuta douglasii.* The young water hemlock plant is cut lengthwise through the stem base. The central main vein runs the length of the leaflet.

periods of difficulty finding the words he wanted. He also complained of short periods in which his mind was a little fuzzy.

Case 2

This 22-year-old man ingested two large rhizomes of the water hemlock plant, *C douglasii*. About one hour after eating the rhizomes, he had severe seizure activity with generalized tonic-clonic movements. As noted in Table 1, he had six seizures between 1400 and 1535 hours before he suffered a cardiopulmonary arrest. After the cardiac arrest, cardiopulmonary resuscitation was done; however, the patient did not respond to the basic life support and died without regaining a pulse or blood pressure.

Discussion

Water hemlock, beaver poison, cowbane, five-finger root, wild carrot, wild parsnip and false parsley are only some of the names commonly applied to several toxic members of the genus *Cicuta*, of the Umbelliferae or carrot family. *Cicuta maculata* is found in eastern North America whereas *C douglasii (C vagans)* is found primarily in the western United States.[2] Because *Cicuta* is a member of the carrot family, the flowers are typically of the umbel type—that is, with compact masses of flower heads. Water hemlock is probably the most poisonous plant that grows in the United States and is known to be extremely toxic to livestock and to humans, with an overall mortality of about 70%.[2] Water hemlock grows in moist ground such as marshes or along rivers or ditches and can easily be confused with wild parsnip, celery, artichokes, sweet potatoes or sweet anise. The root system (Figure 1) consists of a series of large roots (rhizomes) that occur in a bunch attached at a single point to the thickened base of the stem. They look much like a clump of dahlia roots but are smaller. In the spring the roots are the most toxic portion of the plant; as little as one mouthful can kill an adult. Later in the year, the roots are less poisonous, but the leaves and stems contain enough poison to be toxic if ingested.[3]

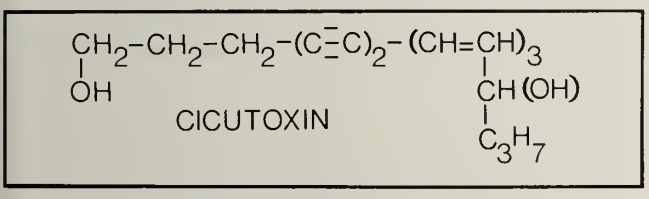

Figure 2.—Cicutoxin structure.

Cicutoxin (Figure 2), the poisonous substance in water hemlock, is a highly unsaturated aliphatic alcohol:

(trans)heptadeca-8:10:12-triene-4:6-diene-1:4 diol

This toxin has a characteristic, dramatic physiologic action that starts 15 to 60 minutes following ingestion.[2]

Poison hemlock, *Conium maculatum*, is a European plant that has been introduced into North America and should not be confused with water hemlock. Poison hemlock and wild carrot both have a long, white, unbranched, turniplike taproot (Figures 3, 4). Poison hemlock was undoubtedly the source of the poison with which Socrates was put to death. It contains several alkaloids that are chemically related to nicotine. Poison hemlock acts by depressing the central nervous system and bringing on paralysis. Death occurs when the muscles of respiration become paralyzed. Figures 3, 4 and 5 show the close resemblance of these plants.

All of the patients who ingested the water hemlock exhibited the early muscarinic and cholinergic symptoms of nausea, abdominal cramping and epigastric distress. In only the two cases reported did the excessive salivation, bronchorrhea, hypotension and seizures that accompany serious poisoning develop. Seizures in both patients started 45 to 60 minutes after ingestion of the water hemlock. The patient in case 2 had five grand mal seizures (Table 1) before suffering cardiopulmonary arrest. During the time between the fourth and fifth seizures, the patient was reported to have a "dream-

Figure 3.—*Conium maculatum*. A young poison hemlock plant with a long, unbranched taproot.

Figure 4.—*Daucus carota*. A young wild carrot plant with a long, unbranched taproot. Note resemblance of taproot to that of poison hemlock.

Figure 5.—*Pastinaca sativa*. Wild parsnip leaves and umbel. Note similarity to water hemlock.

like state with low-volume yelling of unintelligible sounds." The patient in case 1 had five grand mal seizures followed by periods of unconsciousness and stupor. It has previously been reported that the convulsions and spastic-tonic movements observed with cicutoxin poisoning are the result of stimulation of the cholinergic-receptor sites in the brain stem (reticular formation) or of the basal ganglia.[4,5] Because of the severe seizure activity, it was difficult to maintain an airway and both patients were reported to have periods of apnea and cyanosis.

The amount of cicutoxin absorbed appears to be a determinant of the severity of symptoms and of survival. The earliest gastrointestinal response may include vomiting and this may be somewhat protective if the undigested root is removed from the stomach. Numerous authors have reported considerable fluid loss as a result of the violent vomiting and sequestering of fluid in the bowel wall. It has been suggested that this fluid loss results in reduced arterial circulating volume and subsequent hypotension.[6] Although reduced circulating blood volume undoubtedly plays a role in the development of hypotension, it has been shown that an intravenous injection of extract from the water hemlock root diluted with alcohol will result in hypotension within 60 seconds.[7] The hypotensive effect that followed the intravenous injection of the water hemlock extract was followed by the onset of unmistakable convulsive electroencephalographic patterns. This suggests that the cicutoxin has a direct cardiovascular effect that contributes to its toxicity.[7,8]

Treatment of cases of water-hemlock ingestion has been well described by many authors and is not unlike the treatment of any poisoning case that is accompanied by airway obstruction and seizures.[9-13] The airway should be maintained using standard methods including endotracheal intubation, if needed and available. Emesis should be initiated unless a patient is comatose, convulsing or has lost the gag reflex. Seizures should be controlled with intravenous administration of diazepam, and hypotension should be treated by restoring the patient's circulating blood volume with an isotonic solution given intravenously.[3-5]

The above treatment protocol can be carried out in an emergency department; however, if confronted with this problem while on a camping or float trip, it is unlikely that there will be any resources available other than one's knowledge and hands. When it was realized that the "wild parsnip" ingestion was responsible for the seizures, all of the men attempted to induce vomiting without success. They had no syrup of ipecac with them and they did not realize that drinking a liquid dish soap will usually induce vomiting. The usual dose is one tablespoon of soap in eight ounces of water.

Conclusion

As more and more people "return to nature," the number of cases of poisoning that occur from foraging for wild foods is likely to increase. While medical treatment is not likely to be available for these patients, educational programs by poison control centers or physicians should result in a reduction in these poisonings.

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Nineteen Cases of Plague in Arizona

A Spectrum Including Ecthyma Gangrenosum Due to Plague and Plague in Pregnancy

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We review the cases of 19 successfully treated plague patients, with emphasis on the clinical and epidemiologic features of the disease. Proper staining and culturing of bubo aspirates; prompt institution of streptomycin, chloramphenicol or tetracycline therapy in presumptive cases, and supportive care are the crucial factors in the treatment of plague. This disease should be considered in patients in a toxic condition who have lymphadenitis, pneumonia or septic shock and who have been in endemic areas within the past ten days.

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Clinicians should be aware that the same plague that devastated medieval Europe is endemic in the western United States, and at least nine cases of the disease have appeared in other parts of the country as a result of travel of exposed persons from endemic areas.[1-3] Because plague has a wide range of clinical presentations and can cause death within hours of the initial visit to a physician, it is essential to include plague in the differential diagnosis of a wide variety of febrile illnesses and to be sufficiently familiar with and equipped for diagnostic procedures to ensure rapid diagnosis. Three of the nine patients (33%) died in nonendemic areas of the United States compared with a case-fatality ratio of 18% in nontravelers.[2]

The purpose of the report is to make physicians aware of this ancient but still active disease. The death rate is high if diagnosis and appropriate therapy are delayed. From 1966 to May 1983, all 19 plague cases diagnosed among Navajos living on the western Navajo Reservation were successfully treated (a case-fatality rate of 0% compared with the national rate of 14%). We report the clinical features of the 19 cases (Table 1) and describe three of the case histories that show the diversity of the clinical presentations of plague.

Cases were ascertained by reviewing cases reported to the Centers for Disease Control and those admitted to Navajo Area Indian Health Service hospitals. Cases of patients who died out of hospital may not have been ascertained because postmortem blood cultures are only rarely done when Navajos die out of hospital. Case ascertainment of survivors is probably complete because plague is such an unusual and serious disease that physicians are very likely to report it. We considered cases to be confirmed only if *Yersinia pestis* was isolated from clinical specimens or if there was a fourfold or greater rise in passive hemagglutination titer of plague antibody.

Report of Selected Cases

Case 4

A 31-year-old woman in her ninth month of pregnancy was referred to Tuba City (Arizona) Hospital from an outlying clinic in early May 1975 with a one-day history of fever to 40°C (104°F) and severe headache. Plague was suspected when a Giemsa stain of an aspirate of her enlarged, exquisitely tender right axillary lymph nodes showed bipolar rods suggestive of *Y pestis*; streptomycin therapy was begun two hours after admission. When a fetal tachycardia of 200 beats per minute suggested fetal distress, labor was induced with administration of oxytocin. Two and a half hours after antibiotic therapy was started, a male infant with Apgars of 9 and 10 at one and five minutes, respectively, was delivered

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ABBREVIATIONS USED IN TEXT

FA = fluorescent antibody
P_{CO_2} = partial carbon dioxide pressure
P_{O_2} = partial oxygen pressure

without complication and was treated empirically with streptomycin. The maternal lymph node and blood cultures were confirmed as containing *Y pestis* but a cord blood culture was negative for plague. Chloramphenicol was added to the streptomycin treatment of the mother for five days postpartum and she was treated with tetracycline as the sole antibiotic from the fifth to the tenth day of treatment. A mild disseminated intravascular coagulation—manifested by decreased platelets, prolonged partial thromboplastin time and elevated fibrin-degradation products—spontaneously corrected with antibiotic therapy alone. The patient became afebrile on the seventh day of illness, and the lymphadenopathy resolved on the eighth day of illness. Two days later her 2½-year-old daughter was also admitted with a two-day history of fever to 40.2°C (104.°F), headache, vomiting and cough. Plague was diagnosed by culture of an aspirate of her exquisitely tender right axillary lymph nodes, and she was treated with streptomycin. All three patients were well at discharge nine days after the mother's admission. The baby's hemagglutination titer remained negative for plague antibody.

Case 7

A 15-year-old severely ill boy was admitted the end of February 1976 with a three-day history of high fever and severe pain in the axillae. He had skinned a dead rabbit two days before the onset of illness. On admission bilateral, exquisitely tender, enlarged axillary lymph nodes were noted. Wayson stain of a specimen of aspirate showed bipolar rods suggestive of *Y pestis*. Blood cultures and bubo aspirate cultures were all positive for *Y pestis*.

The patient was placed in respiratory isolation and was treated with streptomycin initially. Chloramphenicol was added to the regimen the next day. Six hours after admission the patient began hallucinating, hyperventilating and coughing frothy white sputum. Cerebrospinal fluid was clear with no cells and no bacteria on Gram's stain, and the culture was subsequently negative. A chest radiograph taken ten hours after admission showed a symmetric, mixed pulmonary pattern of both reticular and alveolar densities radiating from the hila bilaterally, borderline cardiomegaly and Kerley B lines (Figure 1.) A sputum specimen contained bipolar rods compatible with *Y pestis* on Wayson stain and was positive for fluorescent antibody (FA), but the organism did not grow on culture. Blood gas determinations done with the patient breathing room air showed a pH of 7.05, a partial oxygen pressure (P_{O_2}) of 36 mm of mercury and a partial carbon

TABLE 1.—*Clinical and Demographic Features of 19 Patients With Plague*

Type
- 15/19 Bubonic (*Yersinia pestis* infection with lymphadenitis; 4/15 with secondary pneumonia)
- 4/19 Septicemic with no adenopathy (1/4 with secondary pneumonia)

Month of Occurrence (# of cases)
- January (2), February (1), April (2), May (7), June (2), July (3), August (1), November (1)

Ages
- Range 2½-78 years
- Average age 25.0 years
- 12/19 16 or younger (pediatric cases)
- 7/19 17 or older (adult cases)

Sex
- 13/19 ♀; 6/19 ♂

Duration of Hospital Stay
- Range 6-28 days (all patients were admitted to hospital)
- Mean 13.8 days

Headache
- 10/19 yes; 6/19 no; 2/19 unknown; 1/19 seizure

Cough
- 3/19 yes; 15/19 no; 1/19 unknown

Skin Manifestations
- 3/19 (1 with ecthyma gangrenosum, 1 with petechiae and 1 with massive cutaneous edema)

Adenitis
- 4/19 no
- 15/19 yes
- 10/15 axillary; 1/15 cervical; 3/15 inguinal; 1/15 femoral

Admission Temperature
- Range 37°C (98.6°F)-40.9°C (105.6°F), only 1 less than 38.3°C (101°F)
- Average 39.4°C (102.9°F)

Admission Leukocyte Count (per μl)
- Range 8,700-48,200
- Average 18,763 (only 2 less than 10,000)

Lowest Platelets (per μl)
- Range 26,000-318,000
- (normal 200,000-350,000)

Sputum Culture
- 1 Positive culture
- 1 Positive Wayson smear and negative culture of specimen taken after 12 h therapy

Bubo Culture
- 14/15 Positive; 1/15 negative (positive FA and positive convalescent PHA 1/512)

Blood Culture
- 15/19 Positive; 3/19 negative; 1/19 not done

Chest X-ray Film
- 12/19 Normal
- 2/19 Definite secondary plague pneumonia (sputum culture or FA test positive for *Y pestis*)
- 3/19 Pneumonia probably due to plague but not confirmed on smear or culture
- 1/19 Minimal pneumonia not thought to be related to plague
- 1/19 Pleural effusion

Prothrombin Time
- Not prolonged in 12 patients tested

Partial Thromboplastin Time
- Prolonged in 3 of 11 patients tested

PHA Titer to Fraction 1 of *Yersinia pestis*
- 2/19 not done; 1/19 negative; 16/19 positive; range 1:4-1:4,096

Antibiotic Treatment
- 15/19 Streptomycin; 8/19 chloramphenicol; 15/19 tetracycline; 3/19 gentamicin sulfate; 1/19 never received recommended antibiotic treatment but recovered.

FA = fluorescent antibody; PHA = passive hemagglutination antibody titer

dioxide pressure (Pco_2) of 19 mm of mercury. Septic shock and adult respiratory distress syndrome developed (Figure 2) as a result of secondary pneumonic plague.

These complications resolved with the administration of high-flow oxygen by mask, dopamine hydrochloride intravenously, methylprednisolone and sodium bicarbonate. He became afebrile on the 24th day of illness and persistent tenderness of axillary nodes gradually resolved without surgical intervention. His chest radiograph became normal on the 15th day of illness. Results of coagulation studies consistent with disseminated intravascular coagulation (see Table 1) were corrected by the end of his course of therapy. Six of the patient's relatives and 17 hospital contacts were located and treated prophylactically with tetracycline because they were at risk for primary pneumonic plague developing. None became ill with plague.

Figure 1.—Erect posteroanterior chest radiograph of patient in case 7 on the third day of illness, ten hours after hospital admission. Symmetric reticular and alveolar densities radiate from the hila bilaterally. The heart is at the upper limits of normal in size. Kerley B lines are very prominent in the lateral costophrenic angles. The radiographic findings are compatible with cardiac decompensation, pulmonary edema and symmetric pulmonic infiltrates of pneumonia.

Figure 2.—An anteroposterior chest radiograph of the patient in case 7 taken on the fourth day of illness, 20 hours after admission, shows more coalescent densities bilaterally, which appear more like pneumonia than pulmonary edema.

Case 12

The patient, a 72-year-old woman, was admitted with a one-day history of vomiting, weakness and fever. She had no adenopathy or skin lesions. The findings on her admission chest radiograph were equivocal, and she was initially treated for pneumonia with a course of cefazolin sodium. On the third day of illness, she became short of breath. A repeat chest radiograph showed pronounced consolidation in both lower lobes. Three pustular lesions also developed in the patient: one on the left posterior thigh, one on the right pubis (Figure 3) and one on the right buttock (Figure 4). At this time, her admission blood culture was reported to be growing Gram-positive rods in chains that could not be identified. Because she remained severely ill, plague was suspected and she was treated with a regimen of chloramphenicol. She was not coughing and was, therefore, not isolated. She became hypotensive (blood pressure 80/60 mm of mercury) and obtunded, and blood gas measurements done while the patient was receiving three liters per minute of oxygen by mask showed a pH of 7.41 and a Po_2 of 53 and Pco_2 of 21 mm of mercury. The lowest platelet count was 46,000 per μl and livedo of the legs developed, but prothrombin and partial thromboplastin times remained normal. Fluid therapy was monitored with a Swan-Ganz catheter, blood pressure was supported with a dopamine drip and her Po_2 was maintained at between 55 and 80 mm of mercury by mask. Gentamicin sulfate was added to the treatment regimen on the fifth day of illness because the patient's condition was not improving and because an etiologic organism had not been identified. On the eighth day, when the patient had improved clinically, cultures of specimens of blood and the pustular skin lesion (taken on day 3) were confirmed to contain *Y pestis* by fluorescent antibody tests.

Administration of chloramphenicol and gentamicin was continued until the 14th day of illness, when the chest radiograph showed clearing, the skin lesions were fading and the platelet count had returned to normal. On the 18th day of illness, her temperature rose to 38.3°C (101°F). Cultures of two blood specimens obtained at that time were negative and no explanation for her fever was found. Tetracycline therapy was added for an additional ten days. She was discharged on the 25th day of illness and has remained well.

Despite the lack of isolation procedures, no secondary cases of plague developed in the staff or visitors. A total of 22 hospital staff members were treated prophylactically with tetracycline (or trimethoprim/sulfamethoxazole if they were pregnant) after the diagnosis of plague was confirmed.

Discussion

Clinical Features

Exquisitely tender lymph nodes are the most typical diagnostic physical features of the cases discussed in this series. Aspiration of affected lymph nodes, culture on blood agar and

staining of the aspirates by Wayson or Giemsa and Gram's methods and by specific fluorescent antibody are the crucial preliminary steps in making a presumptive and, eventually, a confirmatory diagnosis. The FA test requires other qualitative tests including plague susceptibility testing for final confirmation of *Y pestis*. Blood cultures should be done in every suspected case. If pulmonary infection is suspected, sputum should be induced or, in patients unable to cough, tracheal aspiration should be done. The first case of pneumonic plague described here (case 7) showed *Yersinia*-like organisms on sputum smear but a negative sputum culture, probably because antibiotic therapy was started ten hours before the sputum specimen was collected. In such circumstances, slides should be prepared for FA tests that allow a presumptive identification of *Y pestis*. Because *Y pestis* is slow growing even at the optimal temperature of 28°C,[4] FA examination of the sputum will also provide an earlier presumptive test for *Y pestis*.

The thrombocytopenia noted in 9 of the 19 patients and the ecchymoses noted in one patient have been previously described in association with plague.[5] These disorders of coagulation resolved with specific antibiotic therapy alone.

The hypoxia, hypotension and acidosis noted in case 7 responded to the administration of oxygen, dopamine, steroids and bicarbonate. The clinical picture was that of endotoxic shock that occurred soon after streptomycin therapy was begun, possibly as a result of rapid lysis of *Y pestis* by the drug, causing release of endotoxin. Patient 12 had primary septicemic plague, a frequently fatal form of the disease that is difficult to diagnose because the typical buboes are not

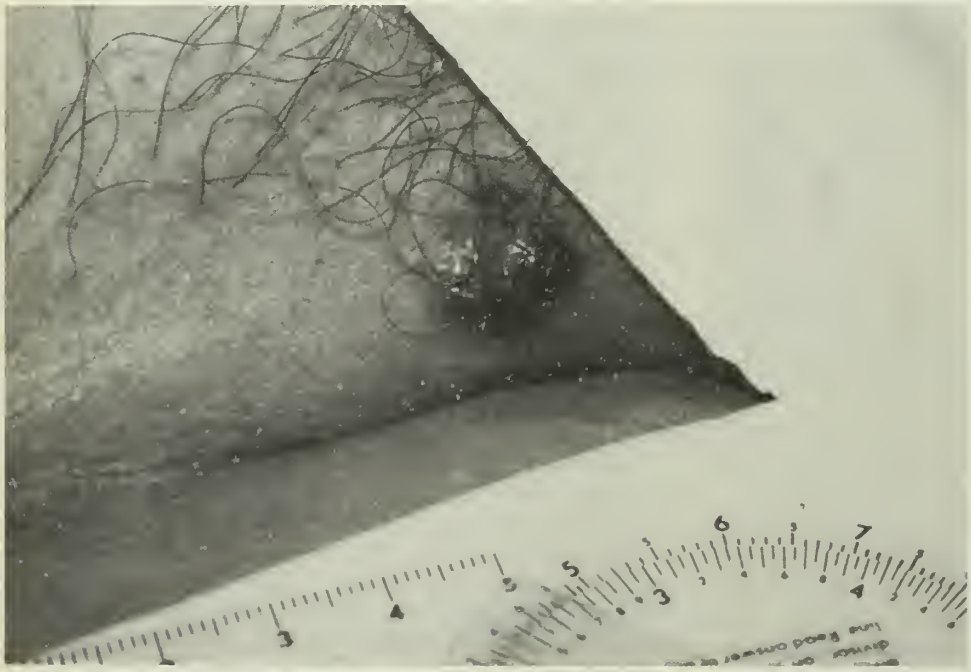

Figure 3.—Confluent hemorrhagic pustules on a violaceous base, an intermediate stage of ecthyma gangrenosum, developed on the right mons pubis of patient 12. The right thigh is below. Scale is in centimeters.

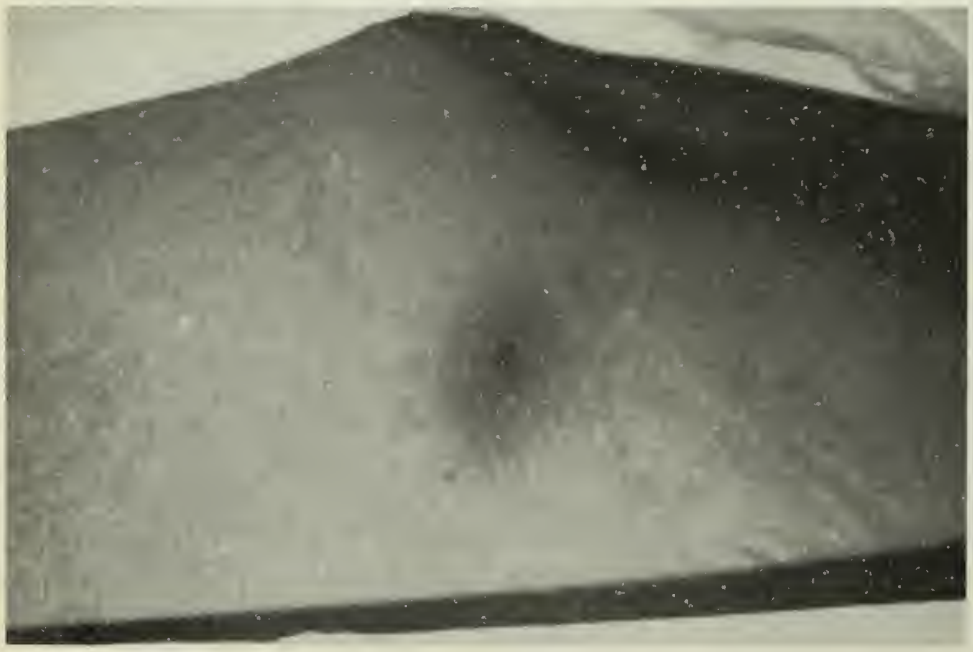

Figure 4.—Final stage of ecthyma gangrenosum, consisting of concentric violaceous rings with an area of central necrosis from the buttock of patient 12. *Yersinia pestis* was aspirated from this 2-cm lesion. Lesions of ecthyma gangrenosum associated with *Pseudomonas* septicemia are also commonly found in the anogenital region and thighs.

present.[6] Probable secondary pneumonic plague and skin lesions characteristic of ecthyma gangrenosum (Figures 3 and 4) developed in this patient. Ecthyma gangrenosum is most frequently associated with *Pseudomonas* infections but can be associated rarely with other Gram-negative infections.[7] Although ecthyma gangrenosum has not been recognized as a complication of *Y pestis* infections, vesicular and pustular skin lesions have been described in some cases of plague.[5] Two cases of "plague carbuncles," which resembled the malignant pustules of anthrax, have been reported.[8] A Vietnamese patient with a fatal case of bubonic plague had lesions similar to those present in our patient. An antemortem skin biopsy specimen of one lesion showed focal epidermal necrosis with subepidermal hemorrhage and fibrin thrombi in the blood vessels. Giemsa stain showed bacillary bacteria embedded in the thrombus but the lesion was not cultured.[5] Specimens from two of the lesions in case 12 were cultured and grew *Y pestis*; this suggests that they were the result of septicemic seeding of the organism in the dermis and epidermis. Biopsies of these lesions were not done.

Case 12 was also unusual in that the organism was initially reported by the laboratory as a Gram-positive rod in chains but was confirmed as *Y pestis* by FA tests six days later. The blood culture from a fatal case of plague in Texas was first reported as growing Gram-positive cocci in pairs.[9] Gram-variable staining may explain these results or they may be due to laboratory error. The index of suspicion for plague was sufficiently high for the patient in case 12 to be treated with chloramphenicol, a treatment that was lifesaving. Isolation of patients with plague is recommended to prevent transmission to medical personnel by aerosol should plague pneumonia develop (see p 646). Although the patient in case 12 was not isolated immediately, she did not cough and no secondary cases developed. It is advisable to obtain a history of possible plague exposure in any severely ill patient who has an unidentifiable organism growing on blood, sputum or bubo culture. If a possibility of exposure to plague exists, appropriate antibiotic therapy and isolation procedures should be initiated until a diagnosis is confirmed.

The patients in cases 7 and 12 showed problems of continued pyrexia after an apparent appropriate response to specific antibiotic therapy. Numerous causes of continued pyrexia must be considered in such circumstances, including unlikely possibilities that a drug-resistant *Y pestis* strain has developed or that the fever is drug-induced. If nosocomial infections are ruled out, such fever may be due to necrosis within a lymph node.[5] Buboes may point and drain spontaneously or require incision and drainage because of pronounced necrosis. Transmission of infection to contacts from such material has not been reported, but draining bubo material should be properly disposed of to prevent this possibility.

Streptomycin is bactericidal for *Y pestis* and is the drug of choice for treatment of plague patients. Chloramphenicol, gentamicin and tetracycline are also effective antibiotics and may be given intravenously in hypotensive patients in whom mobilization of streptomycin given intramuscularly is compromised. Oral tetracycline can be used to complete a full therapeutic ten-day course of therapy after streptomycin, intravenous chloramphenicol or gentamicin has been given for five days in the clinic or hospital. Such a change minimizes the risk of renal and vestibular damage from streptomycin. To our knowledge, no animal studies nor sensitivity testing has been done for sulfamethoxazole-trimethoprim or doxycycline and they are not recommended for treatment because adequate clinical trials have not been done.[10] Although gentamicin has been used successfully as the sole antibiotic in treating plague patients, it is not recommended as a first-line drug because streptomycin is more effective than gentamicin in treating mice experimentally infected with plague.[10]

We attribute our success in treating cases of plague to a high index of suspicion, the use of simple and rapid plague-specific diagnostic tests, promptly instituting recommended antibiotics and providing adequate supportive care. Only one patient did not receive recommended antibiotics—a child with an atypical presentation and clinical course (to be described in a separate case report).

Obstetric Management

In the preantimicrobial era, plague during pregnancy regularly resulted in abortion, and the aborted tissues were occasionally infected with the plague bacillus.[4] In 1903 Jennings reported 10,000 cases of plague, 14 of which occurred during pregnancy.[11] Four of the mothers survived, but spontaneous abortions or stillbirths occurred in 13 of the patients, including the four survivors. One of the 14 patients was near her expected date of delivery. The child was born apparently well, but the mother died of postpartum hemorrhage. Ten hours after the birth, lymphadenopathy was noted in the infant's groins and axillae and it died one day later.[11]

Information is sparse on plague during pregnancy since antimicrobial agents became available. In 1975 and 1976, plague was recognized during pregnancy in three patients; two women, aged 28 and 39, were in their fifth month of gestation.[12,13] Our patient (case 4) was at term when she was infected. Of the patients infected during the second trimester of gestation, one was successfully treated with streptomycin[12] and one received a combination of streptomycin and tetracycline.[13] After normal gestation periods, healthy infants were delivered from each. Because a fetus or infant may be exposed to plague either transplacentally[4] or through contact with maternal blood during the birth process, induction of labor or cesarean section should be considered when fetal distress is noted at 36 or more weeks' gestation in infected mothers. A newborn should be treated empirically.

Radiologic Features

Case 7 shows the need to do an admission chest radiograph and to place all cases of possible plague in respiratory isolation; clinical evidence of respiratory involvement in this patient consisted of coughing, which began six hours after admission. The radiographic appearance of secondary plague pneumonia usually is bilateral alveolar infiltrates.[14] Three of the patients with secondary pneumonic plague described in this report also had patchy areas of parenchymal consolidation on the initial chest radiographs; these areas became more confluent on repeat radiographs 12 or 24 hours later. In case 7, widespread interstitial and patchy alveolar disease characteristic of severe pulmonary edema was more prominent. Subsequent radiographs showed sequential resolution of the extensive patchy air space consolidation, with complete clearing of the infiltrates after 13 days of therapy.

Although patchy pulmonic infiltrates on a chest radio-

graph of a patient who is severely ill can suggest the diagnosis of plague in the proper epidemiologic setting, radiographic findings are not etiologically suggestive but rather provide a valuable index for following therapeutic response.

Epidemiologic Features

Plague remains endemic in the Southwest by epizootics that occur in small rodents.[15,16] From 1965 through June 1983, 197 cases of plague were reported to the Centers for Disease Control from the United States, and 19 of those (9.6%) were from the western Navajo Reservation. A case-fatality rate of 14% occurred nationwide,[17] but there were no deaths in the 19 cases in this report. The mean annual incidence rates per 100,000 population in Arizona, New Mexico and Utah are 1.4 for Indians, 0.1 for non-Indians[17] and 2.6 for the western Navajo Reservation. The Navajo rural life-style brings people into contact with animals or fleas bearing *Y pestis* more frequently than that of other ethnic groups.[18] In 1966 and 1967, 6.8% of 266 dogs in the Tuba City area had titers positive for plague antibody.[19] Although dogs usually do not become ill when infected with plague, they may carry plague-bearing fleas if they have frequent contact with rodents in which plague is endemic.[19] In contrast, rodents usually die when infected. In the Tuba City area, four different species of rodents and a rabbit were positive by culture or FA. Since 1967 prairie-dog colonies on the Navajo Reservation have been mapped and periodically surveyed for "die offs" (high death rates) to detect the presence of *Y pestis*. In this manner resident dogs and prairie-dog colonies have been used as sentinels of human disease on the Navajo Reservation.

Intensive educational programs were begun in the areas where plague was identified. Community residents were assisted in dusting their dogs and cats with flea powder, advised to avoid handling dead rodents and instructed to report to a clinic immediately if signs or symptoms of plague developed.

Four of our patients apparently contracted plague while dissecting rabbits, presumably by direct contact of broken skin with infected rabbit tissues or blood. Most cases of plague that occur in the winter months are caused by direct contact with infected animal tissues.[15] The incidence of human plague is higher in the summer months because the fleas on the animals become more active and the avenues for human contact more frequent.[15] Bubocs occurring on the lower torso, primarily in the groin, are generally considered to result from flea bite. Only rarely is a victim aware of flea bites or the precise source of an offending flea.

The risk of person-to-person transmission is not known but is presumed to be low because the last such transmission in the United States was reported in 1924.[20] However, strict isolation is recommended for the first 48 hours of antibiotic therapy for patients with septicemia and bubonic plague and for 96 hours for those with pneumonic plague to minimize the risk to hospital staff. Plague pneumonia developed in five of our patients (26%), compared with a national rate of 23% since 1975.[21] When plague pneumonia develops before a patient is isolated, tetracycline is the preferred prophylactic drug for adult contacts.[10] Based on experience of treating plague in Vietnam, trimethoprim/sulfamethoxazole is recommended for children younger than 8 years and for pregnant women exposed to pneumonic plague.[10] In the United States in the four years from 1975 to 1979, 16 cases of plague pneumonia were diagnosed, with the result that prophylactic therapy was given to more than 1,400 contacts with no evidence of secondary spread.[21] Prophylaxis is not indicated for contacts of nonpneumonic plague cases but community associates should be kept under surveillance because of the possibility of zoonotic exposures to the same source as the index case.[21] Such a situation occurred when plague developed in the daughter of the patient in case 4.

Conclusion and Summary

These 19 cases of plague illustrate the effectiveness of prompt antibiotic therapy for bubonic, secondary pneumonic and septicemic plague on the basis of a tentative diagnosis by Wayson or Giemsa stain of sputum or lymph node aspirate before the diagnosis is confirmed by fluorescent microscopy or culture. Possible human plague cases should be reported through the local and state health agencies to the Plague Branch, Centers for Disease Control, Fort Collins, Colorado. Consultation will facilitate both patient management and appropriate epidemiologic investigation. Plague patients should be strictly isolated for 48 hours until pneumonic plague has been ruled out. Tetracycline is effective for prophylactic treatment of family and hospital contacts who have not followed isolation precedures for pneumonic plague. Usual supportive measures combined with specific antimicrobial therapy appear to be effective in treating endotoxic shock that complicates plague septicemia. A high index of suspicion is crucial in the successful treatment of a case of plague. Physicians practicing in areas where plague is not endemic need to be aware of the possibility that the disease may be imported by patients who have visited the Southwest or other endemic areas.

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Anorectal and Enteric Infections in Homosexual Men

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Homosexual men are at increased risk for traditional sexually transmitted anorectal infections (gonorrhea, syphilis, venereal warts, herpes and chlamydial infection) and enteric infections characterized by a low infecting inoculum (hepatitis A and B, amebiasis, giardiasis, shigellosis and campylobacteriosis). Infections account for most of the gastrointestinal symptoms in homosexual men seen at sexually transmitted disease clinics, but asymptomatic and polymicrobial infections are also common. Distinguishing three syndromes—proctitis, proctocolitis and enteritis—is clinically useful because these syndromes correlate with specific microorganisms and modes of transmission. A careful anoscopic examination, rectal Gram's stain, cultures for gonorrhea and chlamydia, VDRL and darkfield examination of suspicious lesions should be routinely done when sexually active homosexual men present with unexplained gastrointestinal symptoms. Based on the history, physical examination and initial laboratory studies, patients can usually be classified as having proctitis, proctocolitis or enteritis. This distinction facilitates selection of both confirmatory diagnostic tests and antimicrobial therapy. The effectiveness of empiric treatment regimens for asymptomatic sexual contacts or for symptomatic patients in whom microbiological tests are pending has not been studied.

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Homosexual men have a high incidence not only of anorectal gonorrhea, syphilis, venereal warts and herpes infection[1,2] but also of several enteric infections not traditionally considered sexually transmitted—hepatitis A[3] and B,[4] amebiasis,[5] giardiasis,[6] shigellosis[7] and campylobacteriosis.[8] While these sexually transmitted enteric infections can usually be diagnosed and treated if they are suspected, physicians must be aware of patients' sexual preference and practices, must be attuned to the etiology and spectrum of anorectal and intestinal infections in homosexuals and must have an approach to diagnosis and treatment and to counseling of infected homosexual patients. In this article we will review common sexually transmitted gastrointestinal infections in homosexual men and discuss their diagnosis and management.

Risk Factors

The high risk of acquiring sexually transmitted diseases (STD) for homosexual men arises from several factors, including multiple sexual partners, anonymous partners, frequent asymptomatic infections and specific sexual practices such as rectal intercourse and direct or indirect oral-anal contact.[9] Additionally, many clinics and physicians have limited access to diagnostic laboratory tests for some of these infections, leading to nonspecific treatment, inability to recognize asymptomatic infections and little or no treatment of sexual partners. The combined effects of all these factors make it very difficult to interrupt disease transmission. Knowledge of these risk factors, however, recognition of the clinical syndromes produced by these infections and proper treatment and counseling will help decrease the risk of acquiring and transmitting STD among homosexual men.

Clinical Syndromes

A clinically useful approach to determining the cause of gastrointestinal symptoms in gay men involves classifying patients' presenting complaints into three syndromes—proctitis, proctocolitis and enteritis.[10] Symptoms associated with

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ABBREVIATIONS USED IN TEXT

LGV = lymphogranuloma venereum
PPNG = penicillinase-producing *Neisseria gonorrhoeae*
RPR = rapid plasma reagin
STD = sexually transmitted diseases

proctitis include anorectal pain, mucopurulent or bloody rectal discharge, tenesmus and constipation. Symptoms of enteritis include diarrhea, abdominal pain, bloating, cramping and the absence of anorectal symptoms. Proctocolitis produces overlapping symptoms of both proctitis and enteritis.

Anoscopic or sigmoidoscopic examination helps to classify patients into these three diagnostic categories. Patients with proctitis and proctocolitis usually have rectal exudates or rectal bleeding (or both) on anoscopy. If sigmoidoscopy is done, patients with proctitis have disease limited to the rectum, whereas patients with proctocolitis have disease extending at least into the sigmoid colon. Patients with enteritis usually have normal findings on anoscopy and sigmoidoscopy, but have inflammation of the small intestine or more proximal colon (Table 1).

By classifying patients based on their presenting symptoms and signs into these three syndromes, Quinn, Stamm and co-workers[10] were able to associate each syndrome with certain sexually transmitted diseases. They studied 119 homosexual men presenting to an STD clinic with intestinal symptoms and 75 asymptomatic homosexual men presenting for screening at the same clinic. At least 80% of the symptomatic and 40% of the asymptomatic patients were infected with sexually transmissible enteric or rectal pathogens. *Neisseria gonorrhoeae*, herpes simplex virus, non-lymphogranuloma venereum (LGV) strains of *Chlamydia trachomatis* and *Treponema pallidum* were each associated with signs and symptoms of proctitis (Table 1). *Campylobacter jejuni, Shigella flexneri*, LGV strains of *C trachomatis, Entamoeba histolytica* and *Clostridium difficile* produced the symptoms and signs of proctocolitis. *Giardia lamblia* was associated with enteritis. Of the symptomatic patients, 22% had two or more pathogens detected but only 4% of the asymptomatic men had multiple infections. In this study, abnormal findings on anoscopy or the presence of increased numbers of polymorphonuclear leukocytes on rectal Gram's stain, or both, correlated with proctitis and proctocolitis, even in asymptomatic patients. In dealing with homosexual patients, therefore, physicians must consider not only the presenting spectrum of symptoms and signs produced by individual pathogens, but also the possibility of a polymicrobial infection. The high prevalence of asymptomatic infections in this population also deserves emphasis.

Proctitis and Proctocolitis Caused by Anorectal Pathogens

Neisseria gonorrhoeae

N gonorrhoeae is perhaps the most common STD pathogen seen in gay men.[2] Infection usually occurs by direct inoculation of *N gonorrhoeae* into the rectal mucosa during anal intercourse with an infected partner. Anorectal gonorrhea may be symptomatic or asymptomatic. If symptoms are present, they usually consist of mild anorectal pain, itching and mucopurulent discharge. In some cases, more impressive tenesmus and secondary constipation occur.[10] On anoscopy, findings are usually limited to mucopus in the anal canal, especially in the anal crypts. A rectal Gram's stain aids in the diagnosis if positive, but its sensitivity is only 30% to 40% compared with culture, the confirmatory diagnostic test. Homosexual men with uncomplicated anorectal gonococcal infection should receive aqueous procaine penicillin G, 4.8 million units, plus 1 gram of probenecid. For penicillin-allergic patients, administration of spectinomycin hydrochloride, 2 grams given intramuscularly, is the treatment of choice. All sexual contacts should be examined, cultures done and the person(s) treated, and the patient should be counseled to abstain from sex until he has had a negative culture showing cure. A test-of-cure culture should be done five to ten days after treatment.

Penicillinase-producing *N gonorrhoeae* (PPNG) has been identified in the United States since 1976. PPNG infections do occur in homosexual men, but sustained transmission among them has been infrequent.[11] Because rates vary considerably by locale, physicians should be aware of the prevalence of PPNG in their own communities. The current recommended treatment of uncomplicated cases of anogenital PPNG infection is spectinomycin, 2 grams given intramuscularly, or cefoxitin, 2 grams in a single intramuscular dose, given with probenecid, 1 gram by mouth. Pharyngeal infection can be treated with trimethoprim-sulfamethoxazole (80/400 mg), nine tablets by mouth every day for five days. Test-of-cure cultures and contact tracing and treatment of partners are extremely important to limit transmission of PPNG strains.

TABLE 1.—*Syndromic Classification of Gastrointestinal Infections in Homosexual Men*

Characteristics	Syndromes		
	Proctitis	Proctocolitis	Enteritis
Pathogen	*Neisseria gonorrhoeae*, herpes simplex virus, *Chlamydia trachomatis*, *Treponema pallidum*	*Entamoeba histolytica, Campylobacter jejuni, Shigella, Chlamydia trachomatis*, (LGV type)	*Giardia lamblia*
Mode of transmission	Receptive anal intercourse	Direct or indirect fecal-oral contact	Direct or indirect fecal-oral contact
Symptoms	Anorectal pain, burning, discharge, tenesmus	Symptoms of proctitis plus enteritis, hematochezia	Diarrhea, abdominal pain, cramps, nausea, bloating
Anoscopic findings	Abnormal	Abnormal	Normal
Sigmoidoscopic findings	Normal above 15 cm	Abnormal above 15 cm	Normal

LGV = lymphogranuloma venereum

Chlamydia trachomatis

The spectrum of disease resulting from *C trachomatis* rectal infection ranges from the absence of symptoms to severe granulomatous proctitis, in part dependent on the serovar of the infecting *C trachomatis* strain.[12,13] Strains of the LGV serovars cause more severe disease, often an acute proctocolitis with bloody diarrhea, fever, a mucopurulent rectal discharge and severe tenesmus. Inguinal adenopathy is not as prominent with rectal LGV infections as with genital infections, but may be present. On anoscopy, ulcers may be seen. The findings on rectal biopsy specimens obtained from patients with LGV infection can histologically mimic idiopathic inflammatory bowel disease.[14] In LGV-strain infection, antichlamydial antibody titers as determined by the complement fixation test available in most state laboratories are typically greater than or equal to 1:64.

Infections with non-LGV strains of *C trachomatis* usually produce only mild anorectal symptoms or are asymptomatic. Like *N gonorrhoeae* infections, they usually involve the distal rectal mucosa and anal crypts and are acquired by direct rectal inoculation via anal intercourse with an infected partner. Diagnosis can be confirmed by culture for *C trachomatis*, or can be suspected when a rectal Gram's stain shows persistent polymorphonuclear leukocytes and cultures are negative for gonorrhea.

Infection with *C trachomatis* responds to treatment with tetracycline or doxycycline. A case of non-LGV infection can be treated with a regimen of tetracycline hydrochloride, 500 mg by mouth four times a day for one week, while cases of LGV infection should be treated at least two weeks on the same regimen. Residual strictures or fistulas may require surgical intervention. Alternate regimens for patients with tetracycline intolerance or fixed drug eruptions are listed in Table 2.

Herpes Simplex Virus

Most cases of herpetic proctitis are caused by herpes simplex virus type 2 and are acquired by direct inoculation via rectal intercourse.[15] Primary infection usually produces severe anorectal pain, fever, tenesmus, hematochezia and rectal discharge. Constitutional symptoms include fever, chills, malaise and headache, but rarely stiff neck, photophobia or meningeal signs. Urinary retention, S4-5 dysesthesias and impotence, however, occur in as many as 50% of cases of primary rectal herpes simplex virus infection and are unique clinical findings distinguishing herpes simplex infection from other forms of proctitis. Anoscopy or sigmoidoscopy usually shows intact vesicopustular lesions or shallow ulcers, and a biopsy specimen shows microulcerations, intranuclear inclusions or perivascular lymphocyte cuffing. The characteristic clinical features permit most cases to be diagnosed on clinical grounds alone, but the diagnosis can be confirmed by culture, preferably taken from the base of one or more freshly opened vesicular lesions.

There is no definitive treatment for herpes simplex virus proctitis, though studies are under way with various antiviral agents, including acyclovir. Supportive care, hydration, catheterization for urinary retention and admission to hospital for severe disease are recommended. In severe cases, a therapeutic trial of acyclovir given orally or intravenously may be warranted despite the absence of published information regarding its use. Little is known about the frequency or severity of recurring episodes.

Syphilis

Nearly half of the reported cases of early syphilis in the United States occur in homosexual men.[16] Anorectal chancres usually appear within two to six weeks after exposure by rectal intercourse. Primary anorectal syphilis can be asymptomatic and thus remain unrecognized by a patient or may be painful and misdiagnosed as traumatic lesions, fissures or hemorrhoids. In suspected cases, it is therefore of great importance to examine the perirectal area and anal canal via anoscopy for the lesions of primary syphilis, which may appear as a classic chancre or may mimic polyps, smooth lobulated masses or mucosal ulcerations. Condyloma lata, lesions of secondary syphilis, are also found near or within the anal canal and can easily be confused with anal warts. The lesions, however, are usually teeming with spirochetes, and thus a darkfield examination is positive.

Early syphilis can be diagnosed using anoscopy, darkfield examination of perianal lesions and serology. The VDRL or rapid plasma reagin (RPR) test may be negative in a case of early primary disease, but is positive in virtually all patients

TABLE 2.—*Treatment Regimens for Gastrointestinal Infections in Homosexual Men*

Pathogen	*Treatment Regimen*	*Alternative Regimen*
Neisseria gonorrhoeae	Procaine penicillin G, 4.8 million units given IM, + 1 gram probenecid PO	Spectinomycin hydrochloride, 2 grams IM
Chlamydia trachomatis	Tetracycline, 500 mg PO qid for 7 to 14 d	Erythromycin, 500 mg PO qid for 7 to 14 d
Herpes simplex virus	Supportive, or acyclovir, 400 mg PO qid for 7 d	
Early syphilis	Penicillin G benzathine, 2.4 million units IM	Tetracycline, 500 mg PO qid for 15 d Erythromycin, 500 mg PO qid for 15 d
Campylobacter species	Erythromycin, 500 mg PO qid for 7 d	Tetracycline, 500 mg PO qid for 7 d
Shigella species	Trimethoprim/sulfamethoxazole, 1 tablet (160/800 mg) PO bid for 7 d	Ampicillin, 500 mg PO qid for 7 d Tetracycline, 1.5 grams PO as a single dose
Entamoeba histolytica		
Symptomatic	Metronidazole, 750 mg PO for 5 to 10 d, + iodoquinol, 650 mg PO tid for 20 d	Metronidazole, 750 mg PO tid for 5 to 10 d, or Paromomycin sulfate, 25 to 30 mg/kg/d in 3 divided doses for 7 d
Asymptomatic	Iodoquinol, 650 mg PO tid for 20 d	Diloxanide furoate, 500 mg PO tid for 10 d
Giardia lamblia	Quinacrine hydrochloride, 100 mg PO tid for 7 d	Metronidazole, 250 mg PO tid for 7 d

IM=intramuscularly, PO=orally, qid=4 times a day, bid=twice a day, tid=3 times a day

with secondary syphilis. The fluorescent treponemal antibody-absorption test usually becomes positive before the VDRL, and may thus be useful in patients with suspected early syphilis. If a biopsy of suspicious lesions is done, the specimen should be processed for silver staining or for specific immunofluorescence to *T pallidum* as well as for routine histology.[17] A patient with early syphilis should be treated with penicillin G benzathine, 2.4 million units given intramuscularly at a single session. Penicillin-allergic patients should receive tetracycline hydrochloride, 500 mg by mouth four times a day for 15 days. All contacts should be examined, screened and treated.

Proctocolitis and Enteritis Due to Enteric Pathogens

In the past decade, *Shigella, Giardia, E histolytica, Salmonella* and *Campylobacter* have been identified as enteric pathogens in homosexual men. In some cities, sexually transmitted cases may account for a substantial proportion of all reported cases of certain of these infections. For example, from 30% to 50% of cases of *Shigella* reported to the health departments in New York, San Francisco and Seattle-King County occur in homosexual men.[7,18,19] Sexual activity involving direct or indirect fecal-oral contact is the apparent mode of transmission of these infections, most of which can be transmitted by as few as 10 to 100 organisms.

Shigella

Shigellosis in homosexual men often presents with the classic abrupt onset of nausea, cramping, fever and watery diarrhea containing mucus, blood or pus, but also can be asymptomatic.[7] Sigmoidoscopic examination shows mucosal inflammation and friability. Cultures of stool or rectal swabs on selective media (MacConkey's or Shigella and Salmonella agar) confirm the diagnosis. Treatment includes hydration and antibiotics, generally trimethoprim-sulfamethoxazole, 160/800 mg (double strength) taken orally twice a day for seven days. Ampicillin can also be given but many strains show in vitro resistance in some parts of the country. Although the value of treating sexual contacts of infected gay men is not known, it seems reasonable from a public health point of view to screen and treat partners.

Campylobacter Species

C jejuni has become the most common bacterial cause of acute diarrhea in many communities. *Campylobacter* infection is generally acquired by ingesting contaminated food or water, and sexual transmission among homosexual men by fecal-oral contact has not been as clearly shown as has transmission of *Shigella.*[18] However, recent studies have identified *C jejuni* in symptomatic and asymptomatic homosexual men in higher frequency than in matched groups of heterosexual men. A heterogeneous group of newly described *Campylobacter*-like organisms may also produce diarrhea in gay men.[10,20] Diarrhea, abdominal bloating, mucopurulent rectal discharge or mucus-coated stools have been the most common symptoms and signs in homosexual men with *C jejuni* infection. Anoscopic and sigmoidoscopic findings are similar to those described for shigellosis. Infection can be confirmed using selective culture systems that prevent overgrowth of other fecal flora and provide the necessary microaerophilic environment at 42°C, optimal for *C jejuni.*[21]

Patients with *Campylobacter* infections should be treated with a one-week course of erythromycin, 500 mg taken by mouth four times a day. Treatment may shorten the duration of symptoms and clearly decreases the period of fecal shedding. The management of sexual contacts has not been studied, but they should probably be screened and treated empirically.

Parasitic Infections in Homosexual Men

Giardiasis and amebiasis have become endemic in certain homosexual populations, largely because of the high prevalence of asymptomatic infection in these men combined with the frequent use of sexual practices that involve direct or indirect fecal-oral contact. In cases of *E histolytica* infection, symptoms may be absent or severe, including diarrhea, blood or mucus-coated stools, cramps, bloating and fever. Findings on sigmoidoscopy may be normal or include diffuse inflammation and ulceration of the distal colon. Microscopic identification of trophozoites or cysts in a direct stool smear confirms the diagnosis. Symptomatic patients should be treated with metronidazole hydrochloride, 750 mg given orally three times a day for five to ten days, plus iodoquinol, 650 mg by mouth three times a day for 20 days.[22] Alternative treatment regimens include metronidazole given alone or paromomycin sulfate, 25 to 30 mg per kg in three divided doses for seven days, followed by a luminal amebicide such as iodoquinol if clinical cure is not achieved. The importance of treating asymptomatic cyst passers or sexual partners of proven cases is still unclear, but seems reasonable from a public health point of view. In some studies, however, *E histolytica* strains isolated from asymptomatic homosexual men have been largely nonpathogenic by zymodeme typing, and thus further study of the clinical importance of such infections is needed.[23]

Giardia lamblia infection produces symptoms ranging from mild to severe, with abdominal cramps; bloating; frequent, greasy, loose stools; chronic diarrhea; anorexia, and weight loss. Findings at sigmoidoscopy are generally normal because the organism typically parasitizes the duodenum and jejunum. The diagnosis is confirmed by identifying cysts or trophozoites in direct examinations of stool smears or in duodenal aspirate or biopsy specimens if stool smears are negative. Treatment regimens include quinacrine HCl, 100 mg three times a day for five to seven days, or metronidazole, 250 mg by mouth three times a day for ten days. Sexual partners should be screened and treated.

Three stool specimens should optimally be collected to diagnose parasitic infections in homosexual men. These specimens should be collected two or more days apart and should be delivered to a laboratory within an hour of collection, or should be placed in polyvinyl alcohol and 10% formalin preservative. The patient should not be taking antibiotics, antidiarrheal agents containing bismuth or kaolin, magnesium hydroxide or mineral oil. Barium in the gut lumen also interferes with parasite identification, and thus contrast studies should be done after the patient has collected the stool specimens.

Enterobius vermicularis, Iodamoeba buetschlii and *Dientamoeba fragilis* have also been described as sexually transmitted pathogens in homosexual men, but occur infrequently.[24-26] Various nonpathogenic parasites may also

appear in the stool of homosexual men, including *Entamoeba coli, Entamoeba hartmanni, Endolimax nana* and *Chilomastix mesnili.* At this time, these agents are not considered pathogenic and their presence does not require treatment.

Approach to a Homosexual Patient With Possible Gastrointestinal Infection

Given the polymicrobial nature of sexually transmitted gastrointestinal infections in homosexual men and the similar clinical presentations produced by many of these pathogens, physicians must use a systematic diagnostic approach. Doing cultures and stool examinations for all potential pathogens in each patient is prohibitively expensive and can probably be avoided in most patients if one uses an approach like that outlined in Figure 1.[10]

As always, the history and physical examination provide important clues to the diagnosis. In dealing with homosexual patients, physicians must ask about specific sexual practices, as well as the number of recent sexual contacts, to evaluate the risk of infection. A careful genital examination, including inspection of the perirectal skin, the anus and the anal canal by anoscopy, is indispensable and may identify hidden chancres, ulcers or abscesses, as well as determining the extent and severity of infection.

Selected rapid diagnostic tests should be done during the initial examination. A rectal Gram's stain should be done in all homosexual patients with rectal symptoms and may show intracellular Gram-negative diplococci diagnostic of *N gonorrhoeae.* Even in the absence of gonococci, a Gram's stain that shows one or more polymorphonuclear leukocytes per oil immersion field should strengthen the physician's suspicion of an infectious cause for proctitis or proctocolitis symptoms. The initial laboratory evaluation should always include a VDRL, or an RPR test if the physician is particularly suspicious of syphilis. For all suspicious masses or ulcers, a darkfield examination should be done on fluid exudate. All homosexual patients should have rectal screening cultures for *N gonorrhoeae* and *C trachomatis* (if available) on initial examination. Herpes simplex virus infections can often be diagnosed clinically, but cultures from the base of vesicles or ulcers will provide a definite diagnosis.

Based on the history, physical examination and initial laboratory studies, a physician can usually classify a patient as having proctitis, proctocolitis or enteritis and can treat any pathogens identified in the diagnostic tests outlined above. In addition, stools for enteric-pathogen cultures and ova and parasite examination should be sent for patients with proctocolitis or enteritis. The effectiveness of empiric treatment

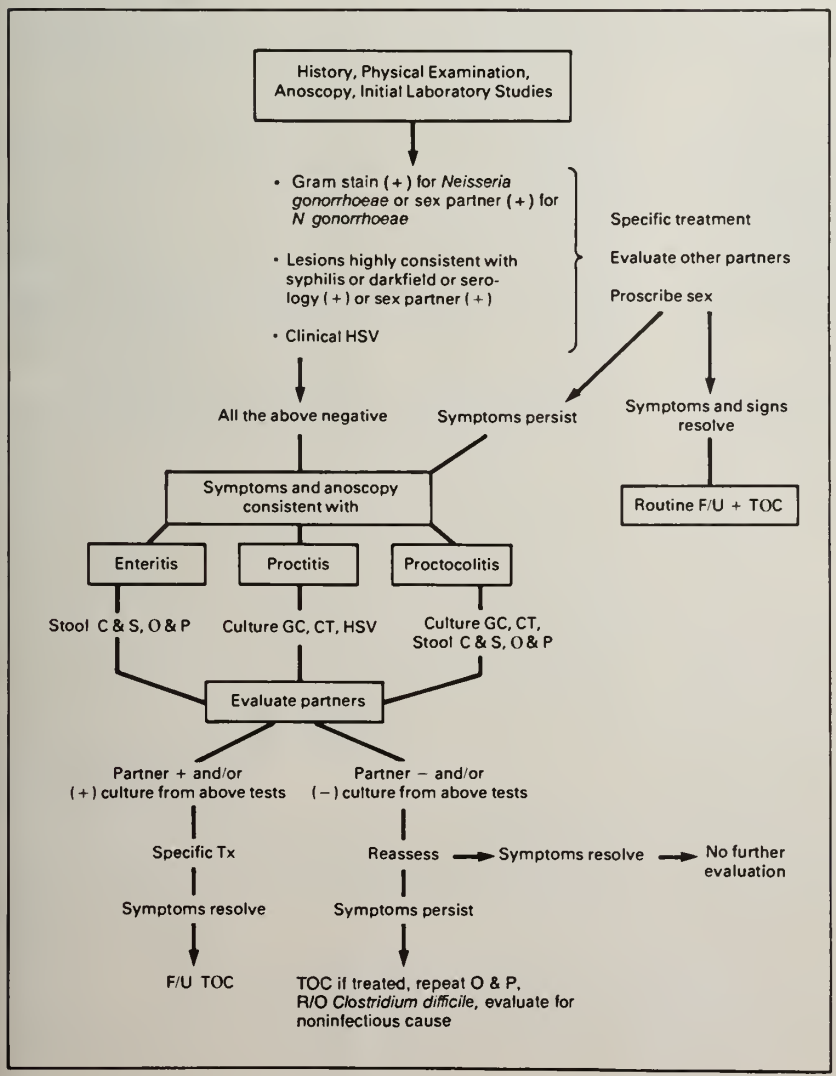
History, Physical Examination, Anoscopy, Initial Laboratory Studies
• Gram stain (+) for Neisseria gonorrhoeae or sex partner (+) for N gonorrhoeae
• Lesions highly consistent with syphilis or darkfield or serology (+) or sex partner (+)
• Clinical HSV
Specific treatment
Evaluate other partners
Proscribe sex
All the above negative
Symptoms persist
Symptoms and signs resolve
Routine F/U + TOC
Symptoms and anoscopy consistent with
Enteritis
Proctitis
Proctocolitis
Stool C & S, O & P
Culture GC, CT, HSV
Culture GC, CT, Stool C & S, O & P
Evaluate partners
Partner + and/or (+) culture from above tests
Partner − and/or (−) culture from above tests
Specific Tx
Reassess
Symptoms resolve
No further evaluation
Symptoms resolve
Symptoms persist
F/U TOC
TOC if treated, repeat O & P, R/O Clostridium difficile, evaluate for noninfectious cause

Figure 1.—Algorithm for managing anorectal or intestinal symptoms or both in homosexually active men (adapted from Quinn et al[10]). HSV = herpes simplex virus, F/U = follow-up, TOC = test of cure [culture], C & S = culture and sensitivity, O & P = ova and parasites, GC = gonococcus [smear], CT = *Chlamydia trachomatis,* Tx = treatment

TABLE 3.—*Possible Noninfectious Causes of Intestinal Symptoms in Homosexual Men*

Ulcerative colitis	Polyps
Crohn's disease	Ulcers
Hemorrhoids	Trauma
Fissures	Foreign bodies
Fistulas	Rectal carcinoma
Irritable bowel syndrome	Lactose intolerance

regimens given while microbiologic test results are pending has not been studied. If symptoms are mild, treatment should be deferred until results are available, and noninfectious causes should also be considered. Alternatively, in patients with more severe symptoms in whom the suspicion of an infectious cause is high, we have used empiric treatment regimens such as aqueous procaine penicillin, 4.8 million units given intramuscularly, plus 1 gram of probenecid given orally, followed by tetracycline, 500 mg by mouth four times a day for one week, for patients with proctitis or proctocolitis, and metronidazole, 250 mg by mouth four times a day for one week, for patients with enteritis symptoms. All patients should be reassessed for resolution of symptoms and signs, and should have test-of-cure evaluations for identified pathogens. Should symptoms persist after appropriate treatment for one infection, other pathogens should be sought. If no pathogens are identified and symptoms persist, the patient may require gastroenterologic workup for possible inflammatory bowel disease or other noninfectious processes (Table 3). Sexual partners should be evaluated and empirically treated for gonorrhea and syphilis if these infections were identified in the index case. For other infections, studies supporting the effectiveness of empiric therapy are lacking, and partners should be evaluated microbiologically and treated only for specific identified infections. Counseling regarding the symptoms of sexually transmitted enteric infection and their modes of transmission should be provided.

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Report From the California Burn Registry—The Causes of Major Burns

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In its first four years of operation, the California Burn Registry recorded 3,332 cases of burns, of which 73.1% were in male and 26.9% were in female patients of all ages. The average total body surface area burned was 15.4 ± 0.3%. Flame burns were the most common (31.4%). Other common sources included scalds (24.5%) and flammable liquids (12.9%). Several other causes were cited with less frequency. Burns taking place at home occurred more commonly than at all other locations combined. In all, 221 deaths (6.6%) were reported, most (66.1%) of which were due to flame burns.

(Bongard FS, Ostrow LB, Sacks ST, et al: Report from the California Burn Registry—The causes of major burns. West J Med 1985 May; 142:653-656)

Deaths and significant morbidity due to major burns have increased considerably over the past several years. More than 100,000 patients annually require admission to hospital for treatment of burn injuries, using approximately 2 million hospital bed-days.[1] About 6,000 civilians in the United States per year die as a result of thermal injury.[2] The combined cost incurred by these patients is in excess of $1 billion.[3] It has been estimated that at least $50,000 is required to manage a patient with a 50% burn.[4]

In spite of improved therapeutic modalities for burn care, the most effective way to reduce burn morbidity and mortality lies in preventive efforts, which in turn depend on a knowledge of the diversity of the causes of burn injury. The California Burn Registry (CBR) was established by state law in 1977 to provide a central facility for collecting, tabulating and disseminating burn-related information in the state. Since the Registry's inception, the records of more than 3,000 patients have been accumulated. Evaluation of individual and collective case records has provided information regarding the epidemiology of burns and fire-related deaths. This report represents a statistical analysis of etiologic data obtained in the first four years of operation of the Registry.

Patients and Methods

Information was collected from 17 participating burn facilities throughout the state of California. Minimum requirements for patient entry into the Registry included evidence of second- or third-degree burn. Those with only first-degree burns were excluded.

Following a patient's admission to a burn unit, or upon initiation of outpatient therapy, a standard coding form was completed (Figure 1). An estimate of burn severity and relevant etiologic and demographic information, when available, were included. Forms were completed by either medical or health-related personnel. After the patient was discharged from a burn unit, or upon completion of outpatient care, the finished forms were sent to the California State Fire Marshal's office, where the sheets were tabulated and stored as coded data. (The California State Fire Marshal's office works with and provides extensive assistance to the Burn Registry.)

Values are expressed as mean ± standard error of the mean. Comparisons were done using the unpaired Student's *t* test and contingency table analysis (χ^2) when appropriate. Statistical significance was assumed for $P < .05$.

Results

From the tabulated data, 3,332 cases were available for analysis. Due to variability in reporting techniques and errors in data entry, not all patients are included in each category.

Of the 3,332 reports, 3,290 contained properly coded information. Among these, 2,405 (73.1%) were of male patients and 885 (26.9%) were of female patients. The average total body surface area (TBSA) burn was 15.4% ± 0.3%. The average second-degree involvement was 12.4% ± 0.2%. Third-degree burns averaged 15.4% ± 0.1%. A total of 221 patients died (6.6%).

Data were examined in relation to the causative agent. Flame burns were most common, causing 31.4% of all inju-

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ABBREVIATIONS USED IN TEXT

CBR = California Burn Registry
TBSA = total body surface area

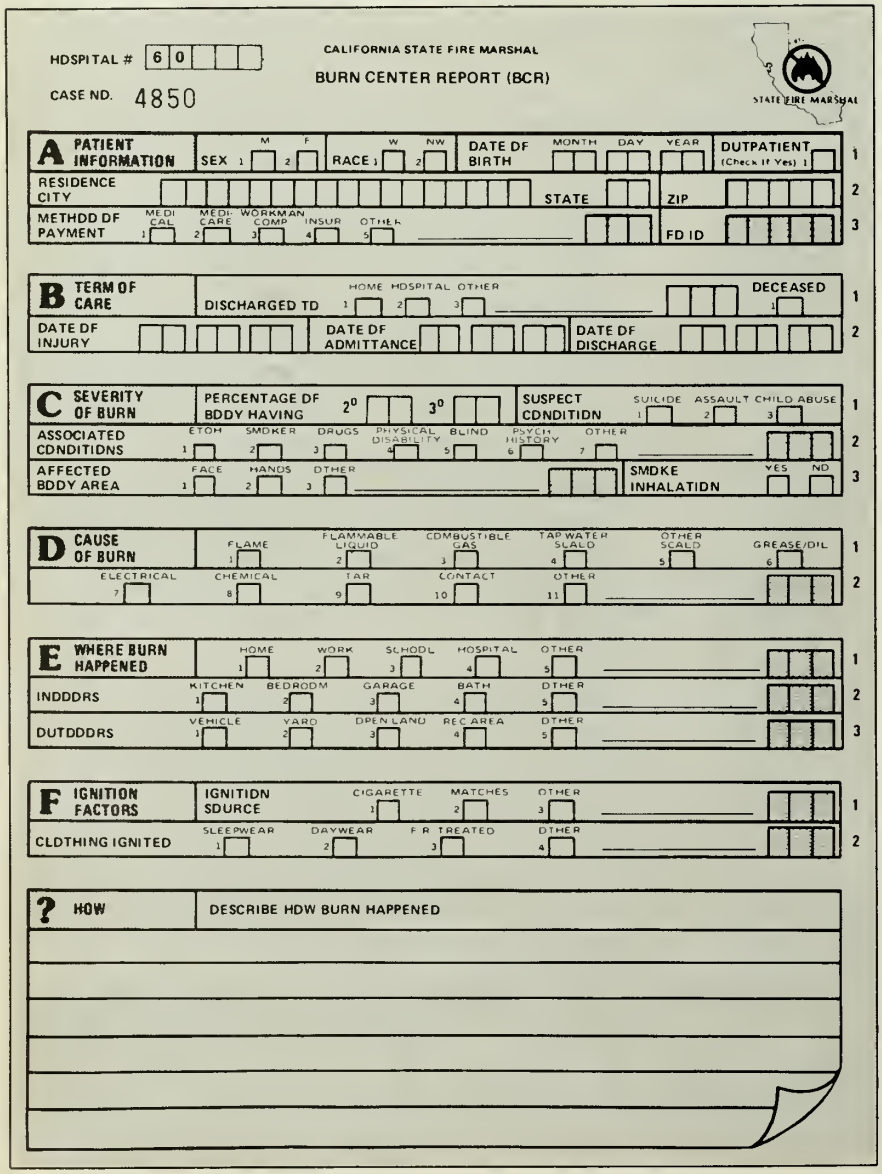
ries. Scalds other than from tap water accounted for 19% of the cases reported. Other significant causes included the following: flammable liquids (12.9%), combustible gas (5.8%), grease (5.6%), tap water scalds (5.5%), tar (4.0%), chemical (3.4%), electrical (3.3%) and all other causes, including contact burns (9.1%) (Figure 2).

The age dependence of each causative agent was examined by sex of the patient. Flame burns, those from flammable liquids and combustible gases and tar burns were most common in the 20- to 29-year age range for both sexes. Chemical burns occurred most frequently in men in the 20- to 29-year decile. There were no reported chemical burns in female patients. Electrical burns were evenly divided among male patients in their third and fourth decades; among female patients, the 20- to 29-year age group predominated. Grease burns were most common in men in the 20- to 30-year age group. Grease burns were most commonly seen in female patients younger than 20 years. Scalds, whether due to tap water or other sources, were predominantly seen in those younger than 10 years, irrespective of gender.

The frequency with which burns occurred was examined with respect to geographic location. Overall, burns sustained at home occurred more commonly than all other locations combined. Within the home, burns took place with the greatest frequency in the kitchen (37.2%). This was followed by the bedroom (12.0%), garage (7.4%) and bathroom (7.0%). Burns at other and unidentified locations in the home accounted for the remainder of residential burns (36.4%).

The geographic location at which a burn occurred was considered with respect to causative agent. Open flame, flammable liquids, combustible gas, grease, tap water and other types of scalds occurred most frequently at home. Chemical, electrical and tar burns occurred most frequently at work.

Burns of the face or hands were frequent findings in this series. A total of 1,223 cases of face burns and 1,473 of hand burns were reported. Face or hand involvement was due most frequently to flame burns (42.5% and 39.7%, respectively).


HDSPITAL # 6 0
CASE ND. 4850
CALIFORNIA STATE FIRE MARSHAL
BURN CENTER REPORT (BCR)
STATE FIRE MARSHAL
A PATIENT INFORMATION
SEX M F
RACE W NW
DATE DF BIRTH MONTH DAY YEAR
DUTPATIENT (Check If Yes)
RESIDENCE CITY
STATE
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METHDD DF PAYMENT MEDI CAL MEDI CARE WORKMAN COMP INSUR OTHER
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B TERM OF CARE
DISCHARGED TD HOME HDSPITAL OTHER
DECEASED
DATE DF INJURY
DATE DF ADMITTANCE
DATE DF DISCHARGE
C SEVERITY OF BURN
PERCENTAGE DF BDDY HAVING 2° 3°
SUSPECT CDNDITIDN SUICIDE ASSAULT CHILD ABUSE
ASSOCIATED CDNDITIDNS ETOH SMDKER DRUGS PHYSICAL DISABILITY BLIND PSYCH HISTORY OTHER
AFFECTED BDDY AREA FACE HANDS DTHER
SMDKE INHALATIDN YES ND
D CAUSE OF BURN
FLAME FLAMMABLE LIQUID COMBUSTIBLE GAS TAP WATER SCALD OTHER SCALD GREASE/OIL
ELECTRICAL CHEMICAL TAR CONTACT OTHER
E WHERE BURN HAPPENED
HOME WORK SCHOOL HOSPITAL OTHER
INDDDRS KITCHEN BEDROOM GARAGE BATH DTHER
DUTDDDRS VEHICLE YARD OPEN LAND REC AREA DTHER
F IGNITION FACTORS
IGNITIDN SDURCE CIGARETTE MATCHES OTHER
CLDTHING IGNITED SLEEPWEAR DAYWEAR F R TREATED DTHER
? HDW
DESCRIBE HDW BURN HAPPENED

Figure 1.—Example of burn center report form.

The other common agents producing face burns were flammable liquids (15.7%), scalds other than tap water (12.8%) and combustible gas (11.4%). Hand burns similarly were caused by flammable liquids (16.1%), combustible gas (9.7%) and scalds other than tap water (9.8%).

Of the 221 deaths (6.6%), the majority were from flame burns (66.1%). Burns from flammable liquids were next in frequency (15.7%), followed by tap water scalds (6.4%), burns by combustible gas (5.9%), other scalds (2.5%), tar (1.7%), electrical (1.3%) and grease burns (0.4%) (Figure 3).

Discussion

The epidemiology of burn morbidity and mortality has been addressed as integral portions of previous reports.[2,5] The large number of patients in this study provides a useful data base for evaluating and contrasting causes of burns. Furthermore, in conjunction with other reports, this series is helpful in planning and establishing prevention efforts on local, state and national levels. This report includes patients of all ages and wide socioeconomic backgrounds. Because of the increasing trend toward outpatient burn care, this subpopulation has been included in our survey. The etiologic information contained in this report is intended for the use of those involved in the treatment and prevention of burn injury.

Data were accumulated from 17 participating burn facilities. Because all burns that occurred in California during our study period are not included and because those at risk were not strictly defined, population-based incidence data are not part of this report. Geographically, all reporting facilities except one were located in the southern two thirds of the state. Hence, reasonable homogeneity exists among environmental conditions. Obvious diversity is present, however, in housing styles, population density and socioeconomic levels. The temperate California climate lends itself to outdoor activities and provides greater exposure to hazards away from home. Additionally, due to the relatively mild winter season, risks from items such as space heaters and other heating-related devices are probably underrepresented in this study, when compared with those reports emanating from harsher climates.

Consistent with the findings of several previous studies,[6-8] burn injuries in male patients predominated over those in female patients. In this series, 73.1% of the patients were male, which is somewhat greater than the 52.4%[6] and 62.3%[8] reported in other large series, but is less than the 78.3% reported by Sanderson and associates.[9] Hence, our sex distribution is within previously defined ranges.

In this study there was a mean TBSA burn of 15.4% ±0.3%. Most studies do not provide a mean TBSA burn but rather report a median burn range percentage. Feck and Baptiste[7] found that more than 90% of their patients in New York had injuries of less than 20% TBSA. Blocker and associates[6] reported that 51.6% of their burn patients had less than 20% TBSA burns, whereas Sanderson and colleagues[9] found 37.6% of their patients to have less than a 20% TBSA burn. The CBR data reveal that 77.4% of the patients had burns of less than 20%, with a median burn of 9.5%. The decreased severity of burns in this study is most likely due to the inclusion of outpatient treated burns, which include less severely injured patients. Other series generally do not report second- and third-degree burns separately and, thus, our median of 9.6% for second-degree burns and 6.3% for third-degree burns is difficult to compare with previous work.

The 221 patients who died represent 6.6% of the population entered into the study. Others have reported from 1.1%[8] to 12.8%[6] mortality rates in in-hospital patients only. Although this study may selectively decrease the total mortality by including outpatients in the denominator, our result falls midway between previously reported mortality rates.

Flame burns typically prevail as the predominant source of mortality in thermal injury. In this series, as in others,

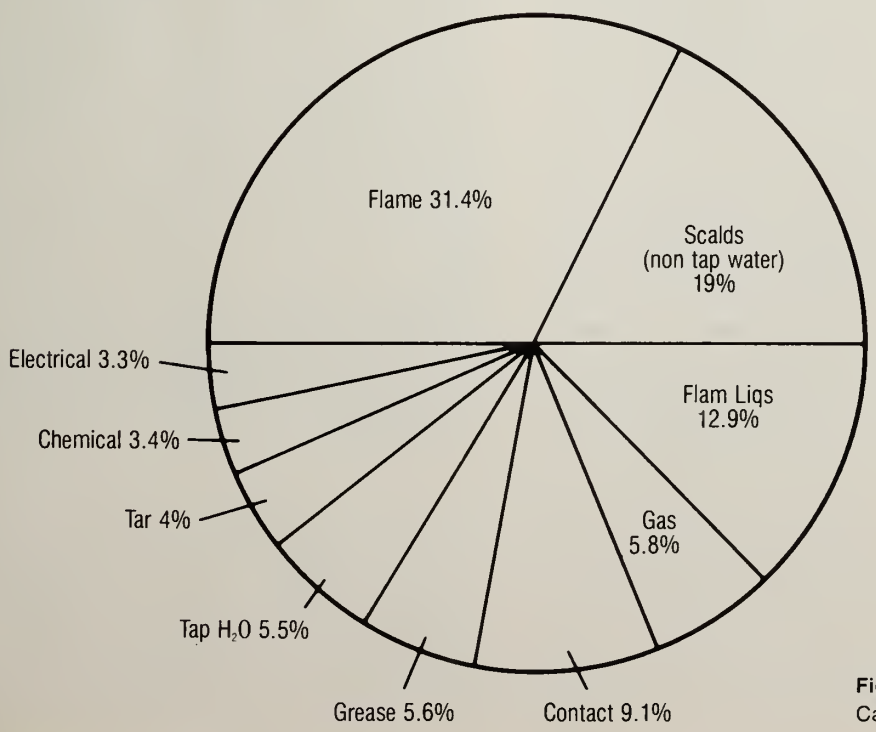

Figure 2.—
Causes of burns in 3,332 cases.

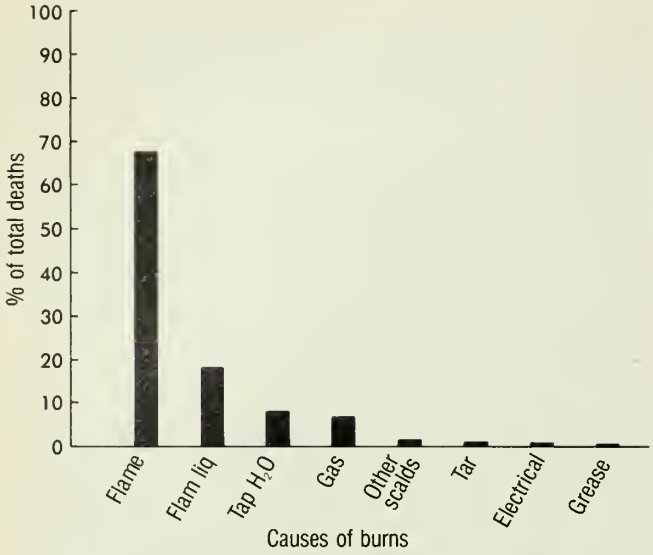

Figure 3.—Causes of death for 221 cases coded in California Burn Registry.

flames cause more deaths than other causes combined. Hamit,[5] in a series of burn patients treated in a community hospital, found that flame burns accounted for only 42.3% of burn cases admitted, but were responsible for 81.5% of deaths. Moyer[10] previously reported that flame burns were more lethal than burns from other causes. In the CBR, flames accounted for 31.4% of the injuries but 66.1% of the deaths. The specific death rate for flame burns was 15.3%, which was higher than that for any other cause (Table 1). In the 30 years since Moyer's report, flame injuries remain the most lethal of all burns.

Flame burns and combined scalds accounted for more than 50% of all burns treated, which is in agreement with previously reported series.[6-8,11] In the present study, flame burns predominated, accounting for 31.4% of all injuries. Our finding is most likely due to the fact that the age group of 20 to 39 years had the most representation. Flame burns occur more frequently in this age group, whereas burns from scalds predominate in the first two decades of life,[12] which was the second most common burn occurrence and the second most common age group to suffer flame burns.

Among the most anatomically and psychologically incapacitating sequelae of burns are injuries of the hands and face. About a third of our patient population had involvement of either or both of these areas. Flame burns were the most commonly cited cause for these injuries. Hand or face burns or both were found in approximately two thirds of all deaths (L.B. Ostrow, MD, F.S. Bongard, MD, S.T. Sacks, PhD, unpublished data, April 1984). Although this is due in part to the fact that involvement of the hands and face often accompanies burns of greater severity, the increase in care required by these injuries complicates patient management. Nutritional, ventilatory and patient personal care are all significantly compromised by these burns.

TABLE 1.—*Burn Cause-Specific Death Rate*

Cause	*Patient Population % of Total N=3,332*	*Cause-Specific Death Rate N=221*
Flame	31.4	15.3%
Scalds other than tap water	19.0	1.0%
Flammable liquids	12.9	8.9%
Combustible gas	5.8	7.4%
Grease	5.6	.6%
Tap water scalds	5.5	8.3%
Tar	4.0	3.1%
Chemical	3.4	.0%
Electrical	3.3	2.7%
Contact and other	9.1	.0%

In this study, the majority of burns occurred at home. This finding, in conjunction with the fact that most were caused by a flame or by a scalding agent, makes clear the need for passive preventive and active educational measures, with emphasis directed to the home. Smoke detectors, hot-water-temperature regulation devices, explosion-resistant fuel tanks on motor vehicles, the use of fire retardants in mattresses and furniture, residential sprinkler systems and fire-resistant cigarettes would all help to reduce burn morbidity and mortality. Only after a thorough understanding of the causes of burns is achieved can effective preventive measures, including environmental modifications and legislation, be implemented.

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Medical Progress

Radiocontrast-Induced Renal Failure

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Review of the literature concerning contrast-induced renal dysfunction shows that the currently used agents are remarkably safe with careful patient selection. Clinically apparent kidney failure after their use is essentially nonexistent in those without preexistent renal insufficiency. The incidence rises rapidly in those with azotemia from any cause, however, and diabetic persons with nephropathy are perhaps at special risk. Vigorous volume expansion is possibly effective as a preventive measure and may attenuate adverse effects in those in whom postcontrast dysfunction occurs. New agents are becoming available. It is not yet known if these will prove safer or cost-effective. They have some experimentally demonstrated and theoretic advantages over the presently used agents.

(Misson RT, Cutler RE: Radiocontrast-induced renal failure [Medical Progress]. West J Med 1985 May; 142:657-664)

In February 1950 a 57-year-old woman was admitted to hospital because of right flank pain present since an injury six weeks earlier. Her blood urea nitrogen (BUN) level was 20 mg per dl. Urography, using "diodone [iodopyracet] fortior" as the contrast medium, was normal. She was sent home. Progressive fatigue and mental deterioration led to readmission on July 11. One week later urography was repeated. The contrast agent was 20 ml of 30% Joduron. She became anuric almost at once and was treated with lumbar anesthesia and infusions of sodium bicarbonate and sulfate. She was given antibiotics by mouth and an emulsion of hypertonic glucose, gum arabic and peanut oil. Despite this treatment, she died on the seventh day after urography with a BUN concentration of 187 mg per dl. At necropsy, her kidneys were large, edematous and pale. Capsular hemorrhages were seen and the proximal tubular epithelium contained many large clear cells.[1]

In an earlier paper, Pendergrass and associates reviewed the records of 661,800 patients who had urographic procedures. There were 26 deaths, which were categorized as early or late. The early deaths were ascribed to anaphylactic shock that did not respond to treatment. The later deaths occurred days to weeks after the procedures. The nephrogram was delayed in some of the urographic studies, suggesting preexistent renal insufficiency.[2]

Since these first reports, much has been written about renal failure associated with contrast agent use. Controversy abounds. While the pathogenesis is imperfectly known, certain physical characteristics of the commonly used agents stand out as potentially hostile to the internal environment. Table 1 summarizes some of the properties of the commonly used contrast media. All agents are viscous and extremely hyperosmolar compared with blood. Much effort has been made to develop media that are more nearly isotonic with plasma and several are now being studied clinically. The literature is replete with expressions of hope that they will prove safer than contrast materials presently in use, although clinically significant renal problems with the current agents are uncommon if proper precautions are observed. In this review we selectively summarize the literature describing contrast-induced renal dysfunction and conclude with a few comments on the new contrast agents.

Incidence of Contrast-Induced Renal Failure

Starting with the report of VanZee and colleagues in 1972, there have been seven retrospective and eight prospective studies exploring the incidence and risk factors associated with contrast-induced renal dysfunction (Table 2).[3-17]

Retrospective Studies

Exclusive of the huge report from the Mayo Clinic[4] in which the criteria for a diagnosis of acute renal failure associated with contrast agents were not specified and mild cases were likely overlooked, the records of 1,216 patients were reviewed and the overall incidence varied from 5% to 17%. In selected subsets of these same patients with certain risk factors, the incidence may be fourfold to fivefold higher. Comparison between studies is difficult because there is no uniform definition of renal "failure" or dysfunction. For example, Swartz and co-workers defined renal failure as "an

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ABBREVIATIONS USED IN TEXT

BUN = blood urea nitrogen
DVI = digital vascular imaging
IVU = urography following intravenous administration of contrast medium
SD = standard deviation

increase in the blood urea nitrogen of 50% or 20 mg/dl, and/or an increase in the serum creatinine of 50% or 1 mg/dl within 48 hours of the angiography procedure."[5] Eisenberg and associates defined renal failure in a prospective study similarly with respect to a change in the BUN concentration, but required only an absolute increase in the serum creatinine level of 1 mg per dl within 24 hours of the procedure.[12] The increase of 50% in the serum creatinine level is omitted, and the follow-up time is halved. As Talner points out in his editorial,[18] a patient whose creatinine level rose from 1.2 to 2.0 mg per dl would be in acute renal failure according to Swartz, but not Eisenberg, and contrast-induced renal failure in any patient whose indices rose slowly would perhaps escape detection if not followed for more than 24 hours.

An interesting possible regional difference in the incidence of renal failure following urography was suggested by Webb and colleagues, publishing in a British journal.[7] The authors regarded a 12% rise in the serum creatinine value as significant. Of their 40 patients, 37 showed "no change in serum creatinine attributable to the urogram." In the other three, clinically unimportant transient increases in serum creatinine occurred. The writers further comment that they "provide a regional service for management of acute renal failure yet have never seen a patient with acute renal failure attributable to urography . . . indicating that our experience of nephrotoxicity of contrast media after urography differs greatly from that in North America."[7]

Prospective Studies

In studies that included both diabetic and nondiabetic patients, the incidence ranged from 0% to 22%. In three studies involving only patients with diabetes or renal insufficiency or both, the incidence was higher, between 6% and 92%.

Clinical Features of Contrast-Induced Renal Dysfunction

The renal dysfunction that follows administration of a contrast agent varies from a transient downturn in renal function to complete irreversible failure. The more serious end of the spectrum is less frequently seen. In his 1980 review, Mudge outlined seven clinical syndromes of contrast-associated renal dysfunction and tabulated the outcomes in 284 cases.[19] The following syndromes were described: (1) decreased glomerular filtration rate with oliguria, (2) decreased glomerular filtration rate without oliguria, (3) decreased glomerular filtration rate with unknown output, (4) acute hypotension with renal insufficiency, (5) a sensitivity-like reaction, (6) medullary necrosis and (7) massive, contrast-associated proteinuria. All but 23 cases are embraced by the first three categories, and in 70% of the 261 episodes, renal function returned to baseline. Some 30% of cases progressed to permanent loss of kidney function with two thirds requiring maintenance dialysis. Oliguric examples outnumbered nonoliguric by three to one. Curiously, the presence of oliguria did not predict a poorer outcome. Recent prospective studies suggest that oliguric failure is less frequent than this.

The six cases of medullary necrosis are interesting. Three of them are documented in a paper by Gilbert and co-workers.[20] All cases were of infants, were fatal and were associated with renal vein thrombosis. Thrombosis of the dural sinuses was present in two of the infants.

TABLE 1.—*Physical Characteristics of Current Urographic Contrast Media*

Product (Manufacturer)	*Anion (Percent)*	*Cation (Percent)*	*Concentration (Percent)*	*Iodine mg/ml*	*Viscosity cps at 37°C*	*Sodium Content mg/ml*	*Osmolarity mosm/liter*
Hypaque 50% (Winthrop)	Diatrizoate	Sodium	50.0	300	2.5	18.0	1,270
Hypaque 60% (Winthrop)	Diatrizoate	Meglumine	60.0	282	4.2	0.02	960
Isopaque 280 (Winthrop)	Metrizoate (46.18)	Meglumine (14.01) Calcium (0.035)	60.2	280	4.06	. . .	1,020
Conray 60 (Mallinckrodt)	Iothalamate	Meglumine	60.0	282	4.1	0.03	1,030
Renografin-60 (Squibb)	Diatrizoate	Meglumine (52) Sodium (8)	60.0	288	3.9	3.76	1,020
Hypaque-M 75% (Winthrop)	Diatrizoate	Meglumine (50) Sodium (25)	75.0	385	8.3	9.0	1,280
Renografin-76 (Squibb)	Diatrizoate	Meglumine (66) Sodium (10)	76.0	370	9.1	4.48	1,270
Renovist (Squibb)	Diatrizoate	Meglumine (34.3) Sodium (35)	70.0	372	6.0	13.5	1,350
Conray-400 (Mallinckrodt)	Iothalamate	Sodium	66.8	400	4.5	24.2	1,660
Hypaque-M 90% (Winthrop)	Diatrizoate	Meglumine (60) Sodium (30)	90.0	462	18.7	10.9	1,430
Isopaque 440 (Winthrop)	Metrizoate (73.0%)	Meglumine (7.59) Sodium (1.66) Calcium (0.078) Magnesium (0.015)	82.3	440	10.4	16.6	1,690
Angio-Conray (Winthrop)	Iothalamate	Sodium	80.0	480	8.4	29.0	2,170

Summary

The most common presentation of contrast-induced renal dysfunction is a modest rise in the serum creatinine concentration that peaks on the third day after the procedure. Urine output is variable and a low fractional excretion of sodium may be seen during oliguria.[3] Preprocedural renal function is regained within ten days in most patients.

Pathology and Pathophysiology

Structural Changes

In 1975 Moreau and colleagues published data obtained from 211 patients who underwent percutaneous renal biopsy following renal arteriography or excretory urography.[21] Typical changes of "osmotic nephrosis" were seen in 47 specimens. This lesion had been described in detail by Allen, who in turn suggested that as early as 1903 Lamy was familiar with its induction by infusion of hypertonic solutions.[22] Moreau and associates described atrophy and patchy necrosis of the proximal tubular epithelium, with cytoplasmic vacuolization. Preexistent renal insufficiency and higher contrast doses seemed associated with a higher incidence of this lesion, with more widespread involvement of proximal tubular cells. Five years later, Moreau and co-workers pointed out that "the new low-osmotic contrast media can induce osmotic nephrosis . . . [as can] . . . dextran which is not an osmotic diuretic."[23] They described the cases of 33 patients, all euvolemic, who underwent percutaneous renal biopsy within 48 hours of urography with metrizamide (a newer agent, used in the United States for myelography but not to any extent for intravascular procedures). It is only slightly hypertonic to plasma (480 mosm per kg of water). Initial renal function was normal in 23 patients and impaired in 10. In six of the normal patients, focal osmotic nephrosis developed. Of the ten patients with preexistent renal insufficiency, a diffuse osmotic nephrosis developed in three and a focal lesion in four. One patient experienced an episode of "oliguric acute renal failure due to urography." Ioxaglate meglumine, another relatively low osmolar agent, induced osmotic nephrosis in four of six patients. The two unaffected persons had normal renal function before urography. The authors believe that "osmotic nephrosis" is not an osmotic lesion at all, but is induced by tubular metabolism of the contrast media—a process in which pinocytosis has a prominent part. They further state that an underlying acute or chronic nephropathy needs to be present

TABLE 2.—*Summary of Incidences of Contrast-Induced Renal Dysfunction (CIRD) Reported in the Literature*

Investigators	Number in Series	Procedure	Criteria (Increase in) Serum Creatinine	Criteria (Increase in) SUN	Time	% CIRD	Comment
Retrospective Studies							
VanZee et al, 1972[3]	377	IVU	1 mg/dl	. . .	≤7 d	O 4.8, N 0.6, A 5.6, D 0.0, DA 58.3	DA: Serum creatinine, 1.4-4.5=50%, >4.5=100%
Diaz-Buxo et al, 1975[4]	115,838	IVU	NS	NS	NS	N 0.0, D 0.2	Study likely to miss subclinical CIRD; 4% had diabetes
Swartz et al, 1978[5]	109	Angiography (1 cholang.)	1 mg/dl or 50%	20 mg/dl or 50%	48 h	O 12.0	All patients with CIRD very ill from nonrenal diseases
Harkonen and Kjellstrand, 1979[6]	24	IVU	0.2 mg/dl	. . .	3-7 d	D 6.3, DA 37.5	All had diabetes; 16 other patients had insufficient data
Webb et al, 1981[7]	40	IVU	12%	. . .	≤7 d	A 7.5	All had baseline serum creatinine >1.8 mg/dl
Cochran et al, 1983[8]	266	Renal angiography	0.3 mg/dl or 20%	. . .	≤5 d	O 16.9	Serum creatinine <1.5=69%; renal dysfunction=80%; 11 had diabetes
Martin-Paredero et al, 1983[9]	400	Angiography	1 mg/dl or 50%	20 mg/dl or 50%	48 h	O 11.3, N 8.2, A 41.7	Higher incidence of CIRD in abdominal studies
Prospective Studies							
Weinrauch et al, 1977[10]	13	Coronary angiography	N/A-all data reported			DA 92.0	All had diabetes with azotemia; CIRD developed in 3 during previous 2 mo
Shafi et al, 1978[11]	40	Drip IVU	25%	. . .		A 61.0, DA 92.0	All had CIRD
Eisenberg et al, 1981[12]	537	Angiography	1 mg/dl	20 mg/dl or 50%	24 h	O 0.0	Vigorous volume expansion
Kumar et al, 1981[13]	100	Angiography	≥0.5 mg/dl		48 h	O 1.0, D 0.0, DA 0.0	24 had diabetes, 6 with azotemia
Rahimi et al, 1981[14]	15	IVU 1 Arteriography	N/A-all data reported			O 0.0	All patients had chronic azotemia; mean serum creatinine, 5.7 mg/dl
Teruel et al, 1981[15]	124	IVU	1 mg/dl or 25%	. . .	. . .	O 21.8, D 16.7	Preparation led to prerenal azotemia; CIRD developed in only DA
D'Elia et al, 1982[16]	378	Nonrenal angiography	≥1 mg/dl	. . .	72 h	O 3.7, N 0.5, A 10.0, D 1.0, DA 23.0	Differences between diabetic and nondiabetic patients with azotemia not significant
Der Shieh et al, 1982[17]	49	IVU	0.5 mg/dl or 25%	. . .	48 h	D 6.1	All diabetic patients with serum creatinine <2.0 mg/dl

SUN=serum urea nitrogen, IVU=intravenous urogram, O=overall incidence, N=normal initial renal function, A=azotemic, D=diabetes without azotemia, DA=diabetes with azotemia, NS=not specified, N/A=not applicable

for the induction of these changes by contrast agents. Last, there is some species specificity to the lesion. In euvolemic, volume-depleted or surgically nephron-reduced rats, this lesion steadfastly refuses to develop despite an iodine dose of 3.75 grams per kg of body weight.

Hemodynamic Changes

Several investigators have examined the effects of radiocontrast administration on renal blood flow. The response is biphasic, a transient vasodilation phase being followed by a longer period of vasoconstriction.[24] Following injection of a bolus of contrast agent, renal blood flow increases rapidly to perhaps 50% above baseline. A swift decline follows; by one minute after injection, the flow is from 20% to 30% below baseline. Over the next ten minutes preinjection blood flow rates are reestablished. Sodium depletion enhances both the degree and the duration of the vasoconstrictive response.[25] Renal blood flow declined three times as much and vasoconstriction lasted twice as long in sodium-depleted dogs. Vasoconstriction is greatly attenuated when intrarenal angiotensin is blocked with saralasin acetate. Workman and colleagues measured aortic and renal venous angiotensin II levels following intra-aortic injection of a contrast agent but they found no changes.[26] They did observe an "unequivocal fall" in prostacyclin levels, the nadir coinciding with the lowest renal blood flow rate. They suggest that prostacyclin modulates the effect of angiotensin, and removal of this modulation by the administration of a contrast agent would leave the effects of normal levels of angiotensin unopposed, hence the effectiveness of angiotensin blockade.

A different mechanism for the reduction of renal blood flow by contrast agents was suggested by Katzberg and coworkers.[27] They suggest that the osmotic effect of the filtered contrast agent causes increased intratubular pressure that outlasts that in the intravascular compartment. Thus, both kidney size and intrarenal pressure increase. Renal perfusion is decreased by direct compression of the glomerular tufts and by increased total renal vascular resistance. They report that the decrease in renal blood flow is amplified by ureteral occlusion, a procedure that further increases intracapsular pressure.

To study the effects of contrast agents in a previously ischemic kidney, Lund and associates induced renal damage in dogs by occluding the renal artery for ten minutes, followed by perfusing with diatrizoate sodium, iopamidol or physiologic saline.[28] Histologic changes were most severe following administration of diatrizoate and least after saline. Cortical blood flow was reduced to the same extent following exposure to all three solutions. This reduction was short-lived, however, and its degree did not correlate with the development or severity of tissue damage. A fascinating and unexpected finding was a significant decrease in cortical blood flow in the contralateral kidney following perfusion with iopamidol. These investigators concluded that "these results indicate that contrast-induced failure is not primarily caused by renal ischemia"—a view that receives firm support elsewhere.[29,30]

Erythrocyte crenation and aggregation have been described following exposure to contrast media, resulting in higher blood viscosity.[31,32] Perfusion studies of dog kidneys comparing contrast agents in saline with contrast agents in whole blood suggest that the rheologic change achieved by the red cells' interaction with a contrast agent contributed greatly to renal damage.[33] This study was conducted using an older agent, sodium acetrizoate, which is very hyperosmolar to plasma and much more viscous than the conventional agents. Altered hemoglobin-oxygen dissociation in the presence of contrast agents has been described that could impair tissue oxygenation.[34]

Intratubular Obstruction

The possibility of intratubular obstruction following administration of contrast agents has been explored by several investigators. Proposed obstructive substances have varied from native or abnormal urinary proteins to crystalline deposits. For example, contrast agents have been shown to increase the secretion of Tamm-Horsfall protein and can cause gelling of Tamm-Horsfall protein in vitro.[35] In addition, normal tubular protein has been found to interact with Bence-Jones proteins with tubular cast formation.[36] It is possible that contrast agents enhance this cast formation, leading to intratubular obstruction.

Contrast media, particularly those used orally for cholecystography, are uricosuric. Iopanoic acid and iopodate promote uricosuria lasting for as long as six days.[37] Crystalluria could thereby be enhanced with subsequent tubular obstruction. Harkonen and Kjellstrand added credence to this when in 1981 they reported biopsy findings consistent with acute uric acid nephropathy in a patient with contrast-induced renal dysfunction.[38] But they also noted reports by other investigators of normal uric acid excretion rates throughout episodes of contrast-induced nephropathy. In 1984 Berkseth and Kjellstrand wrote, "It is unlikely that these effects are . . . important in the genesis of contrast-induced renal failure."[39] As for other possible sources of crystalline deposits, oxalate excretion has almost doubled following administration of a contrast agent.[40]

Summary

The cause of contrast-induced renal failure is unknown. Several possibilities have been explored. Contrast agents are probably tubular toxins, although no specific lesion has been found. Altered hemodynamics due to both dynamic vessel and blood cellular changes may be contributory, as may proteinaceous or crystalline obstruction of the tubules.

Risk Factors and Prevention

Renal Insufficiency

From both retrospective and prospective studies (Table 2), it is apparent that renal insufficiency is associated with a greater risk for renal failure following the use of contrast media. The study reported by D'Elia and associates is an example. In their prospective study of 378 patients undergoing angiography, serial determinations of serum creatinine and urea nitrogen concentrations were made, and 24 hours following the procedure a plain abdominal radiograph was examined for a persistent contrast-enhanced nephrogram, a finding others have reported as a sensitive if somewhat nonspecific marker for contrast-induced renal failure.[41] The authors defined acute renal failure as an "increment of serum creatinine of 1.0 mg/dl or more." About a third of their patients had diabetes mellitus and 26% had been previously exposed to a radiocontrast agent. Of the 378 patients, 29 had

an initial serum creatinine concentration of 1.5 mg per dl or higher and a serum urea nitrogen of 30 mg per dl or higher: the group means were 2.3 mg per dl for creatinine and 47 mg per dl for BUN. Contrast-induced renal dysfunction developed in 33% of the azotemic patients compared with 2% of the remainder. The findings of VanZee and colleagues were similar. Among patients with an initial serum creatinine of less than 1.5 mg per dl, dysfunction developed in only four (1.4%); it was "mild" in three. Of the 76 patients whose initial serum creatinine levels fell between 1.5 and 4.5 mg per dl, 7 (9.2%) showed evidence of postprocedural renal impairment, as did 7 of 18 patients (39%) with initial serum creatinine concentrations of more than 4.5 mg per dl. There are several similar studies reported by others.[5,13]

Cochran, Wong and Roe examined 28 "clinical risk factors previously alluded to in the literature" in 266 patients undergoing angiography.[8] In all, 45 (16.9%) showed acutely decreased renal function defined as an increase in the serum creatinine concentration of 0.3 mg per dl or 20% above baseline. For such small changes to be reliable, a precise creatinine assay with very small interassay variations is needed. The authors found that there was an almost three times greater likelihood of renal dysfunction developing in those whose baseline serum creatinine was 1.5 mg per dl or more. Other less widely accepted conclusions were offered: diatrizoate meglumine was less toxic than the sodium salt; men were 1.5 times more likely than women to display a nephrotoxic response; proteinuria, hypertension and vascular disease were all thought predictive of increased risk. Diabetes mellitus was not mentioned.

While most authors acknowledge the association of preexistent renal insufficiency and contrast-induced renal dysfunction, contrary views are still to be found. This may be related to careful patient selection. For example, a prospective study of 15 patients subjected to urography following administration of high doses of contrast media and 1 patient undergoing selective renal arteriography is reported in the *British Medical Journal*.[14] Serum creatinine concentration (mean ± standard deviation [SD]) before the procedures was 6.4±1.2 and afterwards 6.6±1.1 mg per dl. No episodes of increased tubular enzymuria were found, and no patient had deterioration of the glomerular filtration rate as established by Cr 51 edetate clearance. No patients with diabetes mellitus or myeloma were admitted to this study and "great care was taken to avoid dehydration."

Diabetes Mellitus

Diabetes mellitus is listed in most reviews of contrast-induced renal dysfunction as a risk factor. Coggins and Fang, in a recent book chapter, list risk factors under the headings, "Definite, Probable and Possible"; diabetes mellitus and renal insufficiency are the only disorders listed in the first category.[42] Kirschenbaum and Nissenson regard diabetes mellitus as "one of the most important risk factors."[43] Patients with diabetes without evidence of nephropathy are probably not at high risk, however. VanZee and co-workers found no cases of contrast-induced renal failure among their 19 diabetic patients with initial serum creatinine levels of less than 1.5 mg per dl.[3] Harkonen and Kjellstrand reviewed the records of 40 diabetic patients with serum creatinine concentrations of less than 2 mg per dl who underwent angiography.[6] Of 24 patients, 16 had normal initial serum creatinine concentrations. One patient had an increase in serum creatinine level of 0.4 mg per dl that resolved within a week. The writers concluded that whereas patients with diabetes mellitus with renal insufficiency are at a "high risk of sustaining contrast media induced renal failure," IVU is a "relatively safe procedure in those without evidence of renal impairment."

In the two largest series containing diabetic patients with serum creatinine concentrations of less than 2 mg per dl, VanZee and associates saw no contrast-induced renal deficiency in 19 patients and D'Elia found only a 1% incidence, a rate similar to that in nondiabetic, nonazotemic patients.[3,6,16] Several reports of smaller study groups of exclusively diabetic patients again show the relatively low incidence (0% to 16%) in nonazotemic diabetic persons, but a high incidence (23% to 92%) in those with a serum creatinine concentration of more than 2 mg per dl.[10,11,13,15-17]

The findings of Kamdar and colleagues suggest that evidence of any nephropathy, such as proteinuria, even with a normal serum creatinine concentration, may predispose a diabetic patient to contrast-induced renal dysfunction.[44] In their study, renal failure developed in seven diabetic patients. Six had preexistent renal insufficiency. The single patient with a normal serum creatinine concentration leaked 2.9 grams of urinary protein daily and had a "urinary infection."

Extracellular Volume Depletion

Extracellular volume depletion has long been considered important as a risk factor.[45,46] The remarkable degree of prerenal azotemia seen after the seemingly innocent standard preparation for urography is often forgotten. The report of Teruel and co-workers is therefore instructive. They found an incidence of 21.8% of renal failure in 124 patients after IVU.[15] A quite remarkable feature of this investigation is the careful documenting of changes in serum creatinine levels produced by the patient preparation—an enema, a laxative and 12 hours of fluid restriction. A baseline serum creatinine concentration (mean±SD) in those without chronic renal insufficiency was 0.9±0.3 mg per dl. Following these ministrations it rose to 1.4±1.2 and after the procedure to 1.6±0.9 mg per dl. A similar progression is recorded in those with chronic azotemia—from 4.6±1.8 to 5.5±1.7 to 6.9±2.6 mg per dl, respectively. Although most authorities feel that "fluid deprivation may play a contributory role," the precise role of volume depletion is not universally accepted. Some authors doubt that it constitutes an important risk factor for contrast-induced renal dysfunction.[4,47,48]

Multiple Myeloma

Patients who have multiple myeloma are subject to renal failure for several reasons: volume depletion, hyperuricemia, hypercalcemia, amyloidosis, light-chain nephropathy and a directly toxic effect of Bence-Jones protein. Of itself, this leaves myeloma patients at increased risk for contrast-induced renal dysfunction. Volume depletion before contrast studies has long been recognized as likely to precipitate a very severe form of acute renal failure due to intrarenal obstruction. Mudge cites data suggesting that whereas the incidence of renal failure in a properly prepared myeloma patient may not be excessive, when it occurs it is severe and often irreversible.[19] This dismal prognosis remains unexplained. Berkseth

and Kjellstrand note that many cases of renal deficiency develop in myeloma patients with the use of highly protein-bound contrast agents that were more likely to interact with paraproteins.[39] They believe the incidence of this disorder with the newer agents is low because they have low protein binding.

Contrast Load and Site of Injection

Little evidence supports the contention that the contrast load and the site of injection are clinically important. It is postulated that intra-abdominal angiography, particularly aortography, allows a large volume of contrast medium to be injected into the renal vessels at high pressure. In one analysis a different reason was suggested for the higher incidence of renal failure following these studies: such patients have a higher incidence of preexisting renal disease than those undergoing thoracic or head and neck arteriography.[16] Within the accepted dosing range, the contrast iodine load does not have a high correlation with renal dysfunction. There are some case reports of renal dysfunction developing after an iodine dose as low as 0.5 grams per kg of body weight. Nonetheless, Talner believes the "dose of contrast material is important and should be considered as a risk factor."[18] Cochran, Wong and Roe found a higher incidence of contrast-induced renal dysfunction in patients receiving 2 ml per kg or more of Renografin-76 than in patients getting less.[8] However, they believed the dose used was tied inextricably to other risk factors and were not sure of its independent role. They report also that patients undergoing two studies within 72 hours are almost twice as likely to have renal dysfunction develop after the second study than after the first. In diabetic patients, Weinrauch and colleagues feel the risk of this disorder occurring increases with contrast dose.[10]

Other Factors

Hypertension, advanced age and peripheral vascular disease have not been convincingly shown to be significant risk factors, though of course they could be associated with chronic renal insufficiency.[38] The evidence for hyperuricemia as a risk factor is a little stronger, particularly in the cases of the intravenous (iodipamide) and oral (iopanoic acid) use of cholecystographic agents.[49] The uricosuric potency of iopanoate, for instance, is roughly equal to that of probenecid. Whether diatrizoate is uricosuric is debated. Neither Swartz[5] nor D'Elia[16] support hyperuricemia as a risk factor for acute renal failure following angiography.

Summary

The list of reported risk factors for the development of contrast-induced renal dysfunction is large. It comprises at least the following: renal insufficiency, diabetes mellitus, extracellular volume depletion, multiple myeloma, contrast load and injection site, repeated exposure to contrast agents, previous episodes of renal failure following the use of contrast dye, proteinuria, hypertension, hyperuricemia, advanced age, vascular disease and liver dysfunction. None of these conditions is universally accepted as an independent risk factor, though renal insufficiency probably comes closest. According to Harkonen and Kjellstrand, more than 90% of episodes of contrast-induced renal failure occur in chronically azotemic patients.[38]

Preventing Contrast-Induced Renal Dysfunction

Few prospective studies specifically address the counteraction of risk factors. There is after all little one can do to reverse the effects of renal insufficiency or diabetes mellitus with nephropathy. Extracellular volume expansion as a protective measure was evaluated by Eisenberg and co-workers. Their 537 patients were infused with 800 ml of normal saline during each hour of procedure time. No fluid restrictions were in force before the procedure, and "encouragement of oral or [administration of] parenteral fluids" was ordered afterwards.[12] The average age of the patients was 61 years, and the incidences of diabetes, established renal insufficiency, hyperuricemia, proteinuria and liver dysfunction were comparable to those in other series. In fact, 52% of the patients in this study had at least two risk factors. Renal dysfunction did not develop in any of the patients following procedures carried out under this protocol. The volume of one patient was inadvertently overexpanded and pulmonary edema developed. The authors make the modest claim that while acute renal failure may occasionally occur after angiography, if adequate extracellular volume expansion is maintained, the often quoted incidence of 10% to 15% of contrast-induced renal deficiency is clearly excessive. However, Levitz and Friedman report a case in which volume expansion and an osmotic diuretic were not effective prophylaxis, but the patient was a 64-year-old man with a 24-year history of diabetes mellitus and moderate renal insufficiency (serum creatinine level, 3.8 mg per dl).[50] He was given a saline solution at 100 ml per hour for some hours before the procedure and 25 grams of mannitol during it. Nonetheless, oliguric renal failure developed.

In their prospective study of 40 patients undergoing infusion urography, Shafi and colleagues gave 1,000 ml of 0.45% saline and 5% dextrose solution throughout the night before the procedure, continuing this during urography.[11] Each person received about 1,500 ml of fluid. All patients had preexisting renal insufficiency. Of the 40 patients, 28 had a rise in serum creatinine concentration of more than 25%, but all recovered without dialysis. Baseline serum creatinine concentrations in those in whom renal dysfunction did and did not develop were not different. It was suggested that whereas hydration was not fully protective, it mitigated the effects, resulting in a milder form of contrast-induced renal dysfunction.

Several investigators have proposed that osmotic diuretics, most often mannitol, are protective when given before or during the contrast exposure. Snyder and associates found that intra-aortic administration of mannitol protected against renal dysfunction in dogs from sodium acetrizoate.[51] The same group had previously reported less dramatic protection by giving a solution of 20% glucose and low-molecular-weight dextran. Old and Lehrner reported that 500 ml of 5% mannitol in an isotonic glucose solution given within an hour of a procedure offered similar protection against contrast-induced renal dysfunction in patients.[52]

What reasonable preventive measures might one institute? First and simplest is the avoidance of unnecessary contrast procedures. Volume depletion by aggressive preparation with laxatives, enemas and fluid restriction is unwise. The concomitant use of other nephrotoxic agents should be avoided where possible. In addition to keeping the contrast doses

small, at least three days should be allowed between procedures. If renal failure does develop, the fullest possible recovery should be achieved before permitting further contrast exposure. Additionally, it is clearly sensible to consider those with serum creatinine levels of 2 mg per dl or more (1.5 mg per dl or more with diabetic nephropathy) at particular hazard. Vigorous volume expansion of such patients is recommended. Eisenberg's protocol, while aggressive, remains for the moment the most statistically impressive and serves as a useful departure point. Mannitol and furosemide infusion, although clinically untested, is advocated by Berkseth and Kjellstrand for those having a serum creatinine level of 2 mg per dl or more. They propose giving 100 mg of furosemide for each milligram per deciliter of the serum creatinine.[39] There is a reasonable rationale for this proposal based on prior trials in animal studies using other nephrotoxic models. If used, extracellular volume depletion should be scrupulously avoided by appropriate saline infusion. As always, patients at high risk for contrast-induced renal failure should have their renal function monitored carefully following contrast studies.

The New Agents

Despite the quite remarkable safety and effectiveness of the present agents, great efforts have been made to develop media that have even less potential for harm. As most of the published information about the new agents is technical rather than clinical, it is difficult for the moment to know how safe they are. It is already clear though that some will be more expensive than conventional agents, and their use may be appropriate only in those at particular risk.

The new agents generally are either triiodinated nonionic monomers, or dimers that dissociate into an anion composed of two benzene rings with six iodine atoms, and a cation—usually sodium or methylglucamine (meglumine).[53] They thus provide three iodine atoms per dissolved particle. Conventional agents provide three iodine atoms for each two particles in solution. Figure 1 shows the chemical structures. The new agents provide equally effective iodine concentrations with fewer osmotically active particles in solution. Spataro, Fischer and Boylin have done comparative studies on the urinary excretion of iopamidol (a nonionic monomer), ioxaglate (a dimer) and diatrizoate (a conventional agent).[54] The authors report that at three and five minutes after injection, the urinary concentration of iodine with the new agents is almost twice that with diatrizoate for the same administered iodine load. Total urinary excretion of iodine is similar with all three, showing that the concentration differences depend on the degree of diuresis induced. They concluded that the new agents should "give greater density and enhance radiographic detail. . . . Because of decreased cardiovascular, neurologic, and renal toxicity, higher doses may be possible when necessary."[54] The osmotic effects of new agents have been studied. They alter serum osmolality and hematocrit less than conventional agents.[55,56]

Metrizamide, a nonionic monomer, has been used in this country as a myelographic agent. It is a satisfactory urographic agent, however, and Siegle and colleagues evaluated it as such in 23 children, at a dose of 2.2 ml per kg.[56] All had normal renal function and were not fluid restricted. The radiologist evaluating the studies was not informed of the new agent's use, but in 17 of 23 cases detected it by the excellent opacification. No inspection of postprocedure renal function was reported, but serum osmolality remained unchanged, and there were no adverse reactions or clinically evident renal dysfunction. One child received only 1.5 ml per kg, with "excellent" radiographic results.

The nephrotoxic effect of ionic and nonionic agents has been directly compared.[57] Khoury and co-workers studied changes in renal function in a group of transplant recipients and in a group of potential kidney donors. The agents used were diatrizoate, iopamidol and ioxaglate. Intravenous digital vascular imaging (DVI) was done in the transplant patients, who had varying degrees of allograft dysfunction. The donors, all with normal function, underwent selective renal arteriography. Both conventional and new agents were used in both groups. All patients were "well hydrated." After DVI, no significant changes were seen in plasma creatinine, urinary *N*-acetyl-D-glucosaminidase or β_2-microglobulin. However, significant changes were seen in the patients given conventional arteriography. Serum creatinine levels rose "significantly," as did the incidence of enzymuria, in 13 of 22 patients receiving diatrizoate, but not significantly in those who received a new agent. The authors summarized thus: "Our results indicate that ionic contrast material has consider-

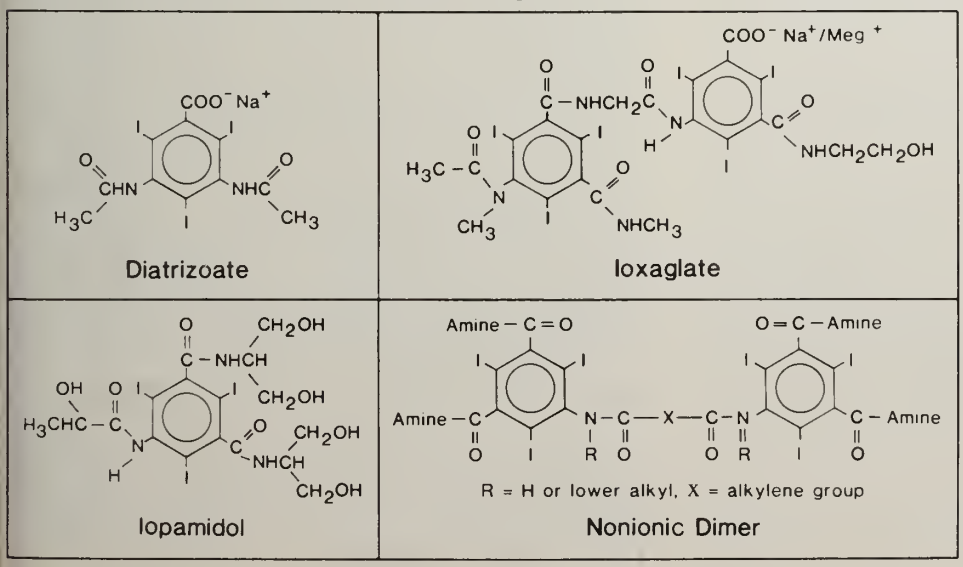

Figure 1.—Chemical structure of diatrizoate, iopamidol, ioxaglate and a nonionic dimer.

ably more nephrotoxic potential than a non-ionic contrast material."[57] Their results may also be interpreted as supporting the view that DVI was less likely than standard angiography to cause renal dysfunction irrespective of the agent used.

One other type of agent is under development. Nonionic dimers are large hydrophilic molecules that do not bind much to protein and are highly water soluble. A review of the physical and pharmacologic aspects of these substances appeared in 1980.[58] The median lethal dose in rats is about twice that of conventional agents and they have roughly half the propensity to crenate erythrocytes in solution for an equivalent iodine load. For 50% activation of human complement during one-hour incubation at body temperature, very high concentrations of dimers are required. No comparative figure is given for conventional agents, but metrizamide produces 50% activation at much lower concentrations. The apparent vascular pain following injection into rat femoral arteries was about the same (0 on a scale of 0 to 10) as with normal saline for both the dimer and metrizamide. Diatrizoate and iothalamate sodium registered 10 each. A solution of 22% sorbitol used for comparison scored between 7 and 8. Intravenous administration of dimers did not cause hypotension or decreased myocardial contractility. The fall in peripheral vascular resistance was less severe and less sustained than that seen with ionic agents. These agents produce "excellent nephrograms." Some dimers are said to accumulate in renal tissue, and while nephrotoxicity is not specifically addressed in the text, the summary of the referenced article notes that it may occur at "very high doses."[58]

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Specialty Conference

Adult Still's Disease—Recognition of a Clinical Syndrome and Recent Experience

Discussant, ERIC B. LARSON, MD, MPH

This discussion was selected from the weekly Grand Rounds in the Department of Medicine, University of Washington School of Medicine, Seattle. Taken from a transcription, it has been edited by Drs Paul G. Ramsey, Assistant Professor of Medicine, and Philip J. Fialkow, Professor and Chair of the Department of Medicine.

ERIC B. LARSON, MD, MPH:* Adult Still's disease has been described in the medical literature for years but has been recognized widely by its current name only in the past decade. Interestingly, a case of an *adult* patient with signs and symptoms of Still's disease was reported in *The Lancet* in 1896, one year before George Still published his classic monograph describing a special form of arthritis in children.[1]

From a clinician's perspective, the major problem has been recognizing that the syndrome of adult Still's disease is a nosologic entity that is diagnostically puzzling and, in some patients, disabling. This problem is well illustrated by the fact that in 1975, the last and only time this topic was presented previously at the University of Washington Medicine Grand Rounds, the presenter realized during the preparation of his talk that adult Still's disease was the correct diagnosis of one puzzling case that he had followed for more than ten years. Because recognizing adult Still's disease has been and continues to be a problem, an appropriate beginning is to review the historical evolution of this disease. This review will take us up to the past decade when the disorder gained wider recognition in the literature. The clinical features of adult Still's disease will be shown by reviewing all papers published in English describing two or more patients.[2-9]

Finally, I shall present details of a series of patients with adult Still's disease[10] seen and followed by physicians associated with the University of Washington to illustrate the nature of this puzzling ailment and its outcome.

History

George Still published his monograph, "On a Form of Chronic Joint Disease in Children," in 1897[11] to describe a disease that he felt deserved special recognition. What is today called Still's disease was based on findings in 12 of the 22 cases reported in that article. Of the 22 cases, Still had seen 19 during a brief two-year residency at Great Ormand Street Infirmary, London.

In Still's original description, he attempted to distinguish a form of chronic joint disease in children from rheumatoid arthritis of adults.[11] Areas of distinction included "affection" of the lymphatic glands, splenic enlargement and pyrexia: "In some cases was sudden hyperpyrexia, lasting an hour or two and then subsiding rapidly. . . . The pyrexial periods are not usually associated with any clinically demonstrable exacerbation of the joint trouble, nor indeed is it possible to usually find any definite cause of the fever." He also described pericardial and pleural effusions and a sex ratio of 1.5 female patients to 1 male patient, compared with the 5:1 ratio described by Garrod[12] in adults with rheumatoid arthritis. Still also argued that the disease is different from other diseases affecting joints in childhood, specifically a form of arthritis that he felt was indistinguishable from adult rheumatoid arthritis (six cases) and a form of post-rheumatic fever arthritis consisting of capsular fibrosis of small joints in the hands and feet—so-called Jaccoud's syndrome. Perhaps one of the most striking features of Still's initial description[11] was an omission. Still did not describe the presence of rash, a key feature in the diagnosis of Still's disease today.

Although adults probably had illnesses similar to some of the cases Still described, the subsequent medical literature does not contain descriptions of cases that clinicians for 70 years considered to be adult Still's disease. However, patients with findings of adult Still's disease were included in cases of undiagnosed fever reported by Reimann and de Bardinis in 1949 in a paper on periodic fever.[13] One patient in this series had transient rash, recurrent fever of short duration to 40°C (104°F), mild leukocytosis, lymphadenitis and intense arthralgia and myalgia. These findings suggest the diagnosis of Still's disease. In addition, reports of cases of fever of unknown origin[14-16] include patients who today might be diagnosed as having adult Still's disease, as do some of the classic series describing patients with rheumatoid arthritis.[17] At the

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same time, in the French and German literature there were occasional reports of an illness called "subsepsis allergica,"[18,19] also called "Wissler's syndrome"[20] and later the Wissler-Fanconi syndrome.[21] This syndrome consists of intermittent fever of extreme magnitude, exanthem, leukocytosis and arthritis. Wissler reviewed his experience with the disease in 1916 and described the cases of two patients, aged 44 and 32 years, in a review article of the syndrome bearing his name.[22]

The first use of the term "adult Still's disease" was by Eric Bywaters, the eminent English rheumatologist, in the 1966 Heberden Oration, "What Is Still's Disease?"[23] In his discussion of the features of Still's disease—fever, rash, lymphadenopathy and splenomegaly—he stated that he had rarely seen adults with such features that he would describe as adult Still's disease.

The paper that most convincingly established Still's disease in adults as a distinct syndrome was published by Bywaters in 1971.[4] It describes 14 cases of which 4 had been presented earlier in a descriptive study of the rash in Still's disease. One important point was that Still's disease in children was a distinct disorder sui generis and not merely an age-related form of adult polyarthritis. Therefore, just as nodular, seropositive, erosive rheumatoid arthritis rarely occurs in children, Still's disease or juvenile rheumatoid arthritis rarely occurs in adults. In 1897 Still stated that Still's disease "is an arthritis in children that is distinct from rheumatoid arthritis,"[11] and Eric Bywaters in 1971 declared that Still's disease is a rare occurrence in adults.[4] It is noteworthy that Still reported 12 cases seen during a two-year residency in a single infirmary, whereas Bywaters collected 14 cases of adult patients over 20 years from referral centers at Taplow and Hammersmith in England. Following Bywaters's papers, adult Still's disease has been recognized widely as a clinical disorder. In fact, series of patients with adult Still's disease have been reported with increasing frequency in North American journals since Bujak and co-workers[3] and Fabricant and colleagues[6] reported series in 1973 and a group of French physicians concluded that the cases of adult patients previously diagnosed as having the Wissler-Fanconi syndrome (subsepsis allergica) had the same disease that Bywaters and others called adult Still's disease.[24,25] From the available literature, a reasonable appreciation of adult Still's disease based on extensive clinical descriptions of patients with this disease can now be obtained.

Literature Review of Adult Still's Disease

Eight papers published in English since 1971 containing two or more cases of adult-onset juvenile rheumatoid arthritis or Still's disease[2-9] provide information about the nature of this syndrome. The clinical features of 59 patients are shown in Table 1. There is a slight female predominance (59%), although one series reports only male patients,[3] another all female patients.[4] It is a disease primarily affecting young adults. The mean age of onset was 24.0 years; median age, 22 years.

Fever, especially high fever, was common, as were rash and arthritis. Less common features included sore throat, adenopathy, splenomegaly, serositis and abdominal pain. However, the frequency with which these findings were reported is variable. The key diagnostic findings were the almost invariable presence of fever, rash and arthritis/arthralgia (the "classical" triad), plus additional but nonspecific and nonlocalizing abnormalities that occurred with variable frequencies. Therefore, the literature shows that adult Still's disease resembles the systemic-onset-type of juvenile rheumatoid arthritis or what has been called Still's-type onset.[26]

TABLE 1.—*Clinical Features of Adult Still's Disease**
(N=59 Patients Except as Noted)

Sex	
Male (%)	41.0
Age	
Mean age at onset (years)	24
Onset at 18-35 yr (%)	86.0
Fever	
≥40°C, N=32 (%)	87.5
>39°C, N=18 (%)	94.4
"Fever," N=9 (%)	77.8
Rash	
Still's, N=49 (%)	93.9
JRA, N=10 (%)	60.0
Arthritis (%)	88.1
Sore throat (%)	49.2
Adenopathy (%)	37.3
Splenomegaly (%)	50.8
Pleuritis/pericarditis (%)	32.2
Abdominal pain (%)	28.6
Hepatic abnormalities, N=45 (%)	33.3

JRA=juvenile rheumatoid arthritis

*From Larson.[10]

Recognition of the seminal clinical features of adult Still's disease is necessary to make the diagnosis. The fever is typically high and spiking, usually quotidian and occasionally double quotidian.[27] The spike occurs in the late afternoon or evening. The duration of fever is typically brief, and the temperature subsides rapidly. Temperature swings of 4°C have been reported to occur in four hours or less.[27]

The rash is perhaps the most helpful feature in the diagnosis of Still's disease, especially when present in association with high fever and arthralgias.[24] It occurs with fever, usually in the evening, and is described as evanescent. It is predominantly a truncal rash, but can spread to the arms and legs including the palms and soles, but usually does not involve the face. The typical eruption is a salmon-pink macular or maculopapular rash beginning as small macules that may coalesce. It usually is not pruritic and may be missed, especially since it occurs in the evening and is evanescent. Patients may not notice it. Koebner's phenomenon is usually present and the rash is more prominent in areas subjected to pressure. The major histologic finding is a polymorphonuclear leukocytic infiltrate in the dermis and perivascular spaces.[4,24]

Musculoskeletal symptoms are the other distinctive features of adult Still's disease. Systemic-onset juvenile rheumatoid arthritis has been called "systemic without arthritis"[26,28] because of the frequent absence of arthritis, as described by Still,[11] during the early phase. All patients, however, do have prominent myalgias (especially involving lumbar, cervical and thigh regions) and polyarthralgias about large joints. These are worse with spiking fevers but may persist between spikes. The arthritis, when present, is usually mild, fleeting

and affects only a few joints. The most commonly affected joints are knees, fingers and wrists.[28] Erosions are uncommon during systemic-type disease and most authors report that there is no consistent relationship between articular manifestations and extraarticular, systemic manifestations. The characteristic features of arthritis in adult Still's disease have been described by Elkon and co-workers (descendant from Bywaters's original report)[29] and Medsger and Christy.[9] The most characteristic feature is the development of carpal ankylosis (Figure 1).[9] Typically, patients have evidence of arthritis in the wrist during acute phases of the disease, but this is usually easily controlled with anti-inflammatory agents. Over a 1½- to 4-year period, the condition progresses to nonerosive ankylosis of the carpal bones, especially those bones bordering the capitate. This occurred in 7 of 13 patients in the Medsger series[9] and 10 of 11 patients observed for 7 to 36 years in England (mean age, 20.2 years).[29] Similar ankylosis has been described in the tarsal bones.[30] The British have also described erosive ankylosis at the interphalangeal joints (sparing the metacarpophalangeal joints and with somewhat unusual ankylosis in the distal interphalangeal joints) and ankylosis of the cervical spine.[29] Once ankylosis occurs, at-

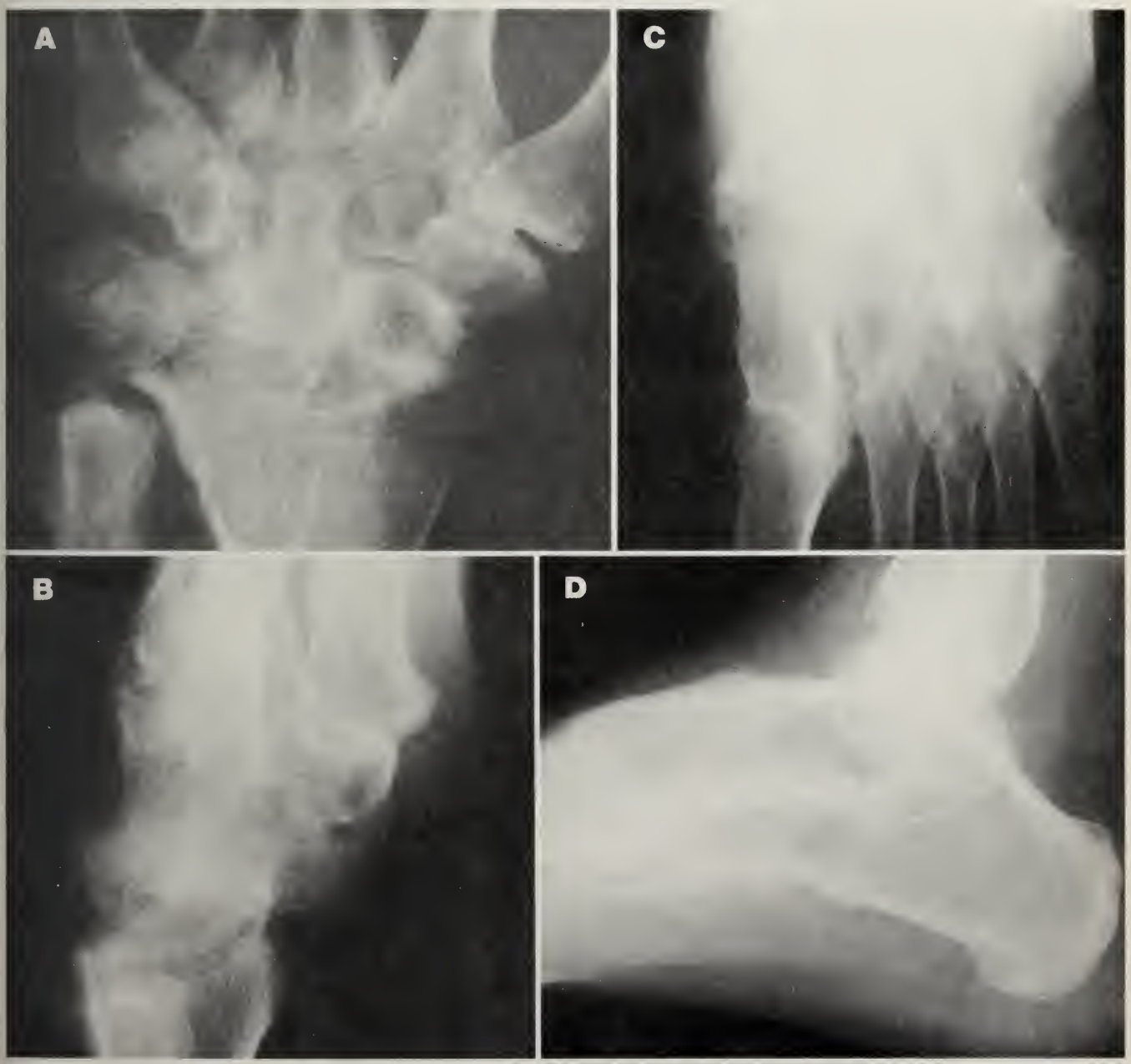

Figure 1.—X-ray films from case 16 with typical changes of adult Still's disease. **A,** Posteroanterior view of the right wrist shows ankylosis of the radial carpal joint and the capitate-lunate joint. The other joints are narrowed and there are areas of erosion. **B,** Lateral view of the right wrist shows the areas of ankylosis. **C,** Anteroposterior view of the tarsal region of the right foot shows complete bony fusion of all of the visualized joints, including the metatarsal-tarsal area. No remaining joint surfaces are identified, other than a small area between the middle and medial cuneiforms. **D,** Lateral view of the right ankle shows bony ankylosis of the subtalar joint. There is also fusion in the area of the midtarsal joints. There is generalized demineralization of the bony structures, with coarsening of the trabecular pattern. (Courtesy of R. F. Kilcoyne, MD, Department of Radiology, University of Washington.)

tacks of arthritis in that region tend to resolve or be minimal and the patient is usually left with painless decreased range of motion.

The other features of adult Still's disease are not as characteristic as the fever, rash and musculoskeletal findings. Sore throat has been described by many authors and is probably related to the disease, since no pathogens have been identified and antistreptolysin O titers do not rise.[4] The lymphadenopathy, hepatomegaly and splenomegaly are nonspecific. At times, these findings have raised suspicion of lymphoma; biopsy specimens, however, have shown only reactive lymphadenitis and, in the liver, focal aggregation of lymphocytes and leukocytes.[3,4] Abdominal pain may be due to mesenteric lymphadenitis and may lead to exploratory laparotomy because of the severity of pain and peritoneal signs. Pleuritis or pericarditis may be recurrent and disabling and pericardial tamponade has been reported.[31,32] Hepatic abnormalities (raised aminotransferase levels) also occur.[33] One case of chronic liver disease and adult Still's disease has been reported.[34] Acute hepatic and renal failure has been described in two patients with adult Still's disease. Both patients were on a regimen of salicylates and indomethacin; one patient died.[33,35]

Laboratory evaluation of patients with suspected adult Still's disease has focused on excluding other diagnostic possibilities. The most common abnormalities in patients with Still's disease are hematologic: leukocytosis (greater than 15,000 per μl in 80% to 90% of patients); normochromic, normocytic anemia (80% to 90%), and an increased erythrocyte sedimentation rate. Tests for rheumatoid factor and antinuclear antibody are consistently negative. Some patients have elevated immunoglobulin levels. All laboratory findings, however, are nonspecific.

Special studies have not offered a consistent pathophysiologic explanation for the syndrome. Circulating immune complexes were found by a staphylococcal A binding assay but not the C1q assay in patients with acute disease.[29] The histology of skin lesions is similar to nonnecrotizing immune complex vasculitis—perivascular neutrophilic infiltrates associated with mast cells with minimal endothelial damage.[29] British authors have suggested that these findings are consistent with immune complexes being deposited in vessel walls that are rapidly removed by neutrophils, followed by mast cell degranulation, neutrophil lysis and macrophage clearance of neutrophil granules.[29]

The University of Washington Experience

In the past 13 years, 17 patients at the University of Washington have been diagnosed as having adult Still's disease. This series of patients has been reported recently in a review article.[10] Six were from an ongoing series of patients with fever of undetermined origin. The other 11 cases came from records that were kindly provided by a number of people.* The case definition was that of Medsger and Christy[9]: (1) high spiking fever without known cause; (2) arthralgias or arthritis (or both) at some time during the illness; (3) serologic tests normal for rheumatoid factor and antinuclear antibodies, and, in addition, at least two of the following features: leukocytosis, evanescent macular or maculopapular rash, serositis (pleuritis, pericarditis); hepatomegaly; splenomegaly, and generalized adenopathy.

Of the 17 patients, 7 were women. The age at which a patient presented for evaluation to a physician varied from 21 to 68 years; 13 were in the age range of 21 to 32 years, with an overall mean age of 32.7 years. In 10 patients, the reason for evaluation was fever of undetermined origin. In the others, fever was present with other symptoms or had occurred in the past. All patients in whom fever was carefully documented had temperatures above 39°C; the mean temperature peak was 39.8°C. The fever pattern was typically quotidian or double quotidian, with a spike occurring in the late afternoon or early evening (Figure 2).

A past history of febrile illness of unknown cause was of particular importance for diagnosis. Twelve patients had had previous episodes of a febrile illness. Although detailed rec-

*These include Drs Robert Willkens, L. Andrew Healey, Gordon L. Starkebaum, Dick Newton, Woodruff Emlen, Arthur Resnick, Oliver Press, Harvey Featherstone and Dennis Boulware.

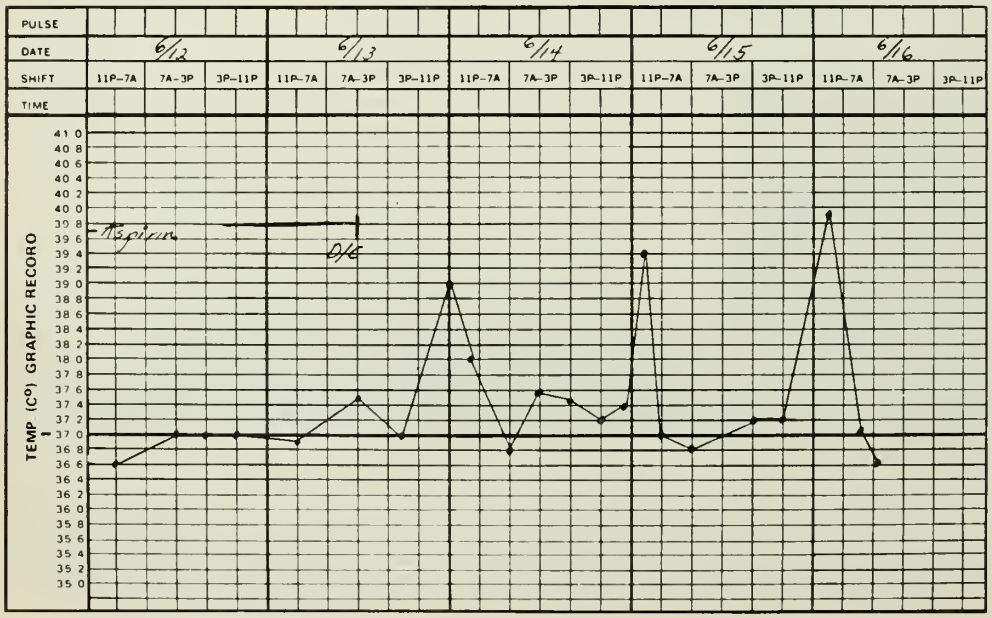

Figure 2.—Fever curve from case 3. After treatment with aspirin (5,280 mg a day) was discontinued, the patient had a spiking fever each evening (quotidian pattern) accompanied by transient rash.

TABLE 2.—*Clinical Features, Treatment and Follow-up of University of Washington Patients**

Case Number	Sex	Duration of Follow-up (yr)	Age at Onset (yr)	Age at Evaluation (yr)	Reason for Evaluation	Initial Clinical Features: Musculoskeletal	Initial Clinical Features: Rash	Initial Clinical Features: Other†	Treatment and Response After Evaluation	Subsequent Complications	Treatment and Response
1	♀	12	16	26	Fever	Monoarticular hip, arthritis	Present in past	H,S	Afebrile on high-dose ASA	Active, deforming polyarthritis	Corrective operations (hips, knees, hands), ASA, steroids; chronic arthritis
2	♂	8	17 (FUO)	21	Fever	Pauciarticular	–	L	ASA, steroids caused remission	Sporadic pauciarticular arthritis	ASA, indomethacin controls arthritis
3	♂	6	20	30	Fever	Pauciarticular arthritis of elbow, wrist	+	L,P	Prednisone 40 mg/d during evaluation; addition of indomethacin controlled attack	Recurrent pauciarticular disease	Indomethacin plus alternate-day steroids for control
4	♂	3	12 ("Rheumatic fever")	30	Fever	Intense myalgias	+	S,L,P	ASA, prednisone reduced fever	Recurrent pauciarticular disease	High-dose ASA effective; poor compliance
5	♂	3	49	49	Fever	Intense arthralgias	+	H,S	Initially indomethacin effective, but eventually high-dose prednisone (120 mg/d) required to control fever	Recurrent fever, arthralgias	Does well on alternate-day prednisone, 10-40 mg every other day; ibuprofen controls arthralgias
6	♂	2.5	28	28	Fever	Arthralgias, shoulder tenderness	+	H,L,P	Indomethacin controlled symptoms	None, illness resolved after 4 mo	No recurrence
7	♂	2.5	64	68	Fever	Arthralgias of shoulders, wrist	+	S,L,P	Fenoprofen effective transiently; prednisone (40 mg/d) needed for control	Recurrences when prednisone dosage tapered	Alternate-day prednisone most effective; chronic neutropenia without serious infections
8	♂	1	Uncertain—7, pericarditis; 17, myocarditis	32	Fever, chest pain	Myalgias, muscle tenderness	+	H,S,L,P	Prednisone for pericarditis, fever	None	Alternative-day prednisone currently effective; by history, acute episodes are widely spaced
9	♀	1.5	44	44	Fever	Intense diffuse myalgia, polyarthralgia	+	S,L	High-dose ASA, indomethacin effective	None	Receiving no treatment
10	♂	1	24	24	Fever	Pauciarticular arthritis of knee, ankle	+ (Papular)	. . .	High-dose ASA effective	One recurrence 3 mo later	Receiving no treatment
11	♀	4	42	45	Arthritis	Pauciarticular arthritis of wrist, knee	+	. . .	Outpatient only; NSAID effective	Smoldering polyarthritis	No recurrence of fever after course of gold; requires anti-inflammatory treatment long term
12	♀	8	Uncertain 12	27	Fever, arthritis	Pauciarticular arthritis of wrist, knees	Present in past	L,P	Indomethacin, prednisone controlled fever	Deforming, erosive polyarticular arthritis	Has had bilateral hip replacements
13	♂	28	27	29 (in 1955)	Serositis, arthritis, fever	Migratory pauciarticular arthritis	+	L,P	Steroids used in 1955 attack and later	Smoldering polyarthritis, occasionally with fever	Gold effective transiently; taking low-dose prednisone (5-7.5 mg a day) and ASA
14	♀	4	16	29	Arthritis	Elbow monarthritis	–	L (S age 16)	NSAID effective	Recurrent monarthritis	Various NSAID effective, splenectomy during episode at age 16
15	♀	3	22	24	Fever, rash	Arthralgias, then polyarthritis	+	H,S,L	Arthritis not helped by anything except steroids	Proliferative polyarthritis	Good response to gold but side effects; taking methotrexate
16	♂	2	20	27	Arthritis	Pauciarticular arthritis of wrist, MTP joint	?	. . .	NSAID initially effective	Carpal ankylosis, tarsal erosions	Improved with gold therapy; Laotian with scant history
17	♀	1.5	Uncertain—17, rheumatic fever	24	Arthritis	Monoarticular, then polyarticular arthritis, myalgias	+	L	Sulindac effective; side effects limited to use of ASA	None	Symptoms during 2 episodes controlled with sulindac; decreased ROM in both wrists

ASA=aspirin, acetylsalicylic acid; FUO=fever of undetermined origin; MTP=metatarsophalangeal; NSAID= nonsteroidal anti-inflammatory drugs; ROM=range of motion; –=no, +=yes

*Other details concerning these patients have been published recently.[10]

†H=hepatomegaly, S=splenomegaly, L=lymphadenopathy, P=pleuritis or pericarditis.

ords were typically not available at the time of the evaluation, a patient was usually able to provide enough information to suggest the possibility that the febrile episodes represented earlier attacks of Still's disease. In two patients, the diagnosis was made on the basis of "typical arthritis," without fever or systemic symptoms; both had a history of a Still's-type presentation occurring several years before the diagnostic evaluation.

Arthritis was present at the initial evaluation in 11 of 17 patients. The other six patients had intense arthralgias and myalgias. Other features included rash (14/17), sore throat 6/10), abdominal pain (6/17), hepatomegaly (5/17), splenomegaly (8/17) and adenopathy (11/17). Enlargement of at least one organ of the reticuloendothelial system was present in 13 of the 17 cases. Evidence of serositis was found in seven cases. Common laboratory abnormalities included anemia, leukocytosis, abnormal hepatic enzymes and a rapid sedimentation rate.

The diagnosis of adult Still's disease was eventually made in a *positive* fashion in all cases. Typically, patients received extensive evaluation and often received courses of antibiotics without effect. However, once a diagnosis of Still's disease was considered, it could be made using established criteria, especially when rash was observed or a history of a previous episode was elicited carefully. The consideration that a patient had Still's disease often eliminated the need to consider other illnesses and made the diagnostic workup less tedious. None of the patients had evidence of coexistent bacterial infection; two had positive delayed results on hypersensitivity skin testing for tuberculosis; none had evidence of a reactive arthritis.

Management and Prognosis of Cases of Adult Still's Disease

Evaluating the response to treatment in our patients was complicated by empiric therapeutic trials before diagnosis, dose changes and side effects of anti-inflammatory drugs. The mainstay of therapy was high-dose salicylates. Anecdotes in the pediatric literature describe patients with fever receiving 2.4 grams of aspirin per day who had remission when the dose was increased to 3.0 grams per day.[36] Similarly, in some of our patients a sufficiently high dose seemed to be critical. Salicylate levels should be in the anti-inflammatory range and several authors state that serum concentrations should be at least 25 mg per dl or more before one concludes that giving salicylates is ineffective. Compared with internists, pediatricians seem more likely to use high doses of aspirin and aspirin alternatives like choline or sodium salicylate.

Nonsteroidal anti-inflammatory agents have also been effective. The use of indomethacin, 100 to 200 mg a day given in divided doses, was recommended by Bujak and colleagues in 1973.[3] In the University of Washington patients, one person with fever and systemic symptoms receiving as much as 1 mg per kg per day of prednisone had defervescence and relief of musculoskeletal symptoms only when indomethacin was added to the prednisone regimen. Other newer nonsteroidal anti-inflammatory agents are being used more frequently; fenoprofen, sulindac and naproxen were each effective in relieving fever and systemic symptoms in some patients.

The use of corticosteroids may be necessary to control fever in some patients. Half of our patients were treated with steroids and two required dosages in excess of 100 mg of prednisone per day. These results are comparable to the experience of Bujak and associates[3] in which 60% of patients were eventually treated with steroids, and of Bywaters,[4] who treated 53.8% of his patients with steroids. For most patients, steroids in high daily doses for long periods were not required but side effects including cushingoid habitus, diabetes, infection, acne and osteoporosis have occurred. In our series, several patients experienced possibly avoidable side effects from long-term steroid therapy before the correct diagnosis of adult Still's disease was determined.

A good strategy for minimizing side effects is to administer steroids on alternate days. Bujak and the National Institutes of Health group[3] have recommended a treatment strategy combining high-dose alternate-day prednisone with aspirin or indomethacin coverage in patients whose systemic symptoms are not controlled with nonsteroidal anti-inflammatory drugs. Most patients on alternate-day steroid doses require concomitant treatment with salicylate or another agent for fever. A few patients described in the literature did not have relief of systemic symptoms with high-dose steroids and required cytotoxic therapy.[8] This did not occur in our patients and has been reported by only one other group.[8]

The initial reports of adult Still's disease emphasized the relative benignity of the disease.[3,4,6] The systemic features were controllable and usually lasted for less than six months. Arthritis was said to be mild and less severe than in cases of adult rheumatoid arthritis. However, the disease probably has a more ominous prognosis than originally appreciated.[37] Complications include pericardial tamponade[31,32] and amyloidosis,[38] a well-recognized complication of juvenile rheumatoid arthritis. Interestingly, iridocyclitis is apparently not a problem in adults.[39]

The experience with adult Still's disease in our community is summarized in Table 2. Approximately 20% of patients appear to have self-limited systemic-type disease, although none of these patients has been followed for more than 2½ years. Recurrences or arthritis could still occur in this group. A few patients have systemic recurrence as a major problem. Pauciarticular disease is a recurrent problem with or without sporadic fever in about a third of patients. Salicylates and other nonsteroidal anti-inflammatory drugs are usually effective in this group and steroids are not required or indicated. Finally, in a third of our patients, chronic polyarthritis developed that was asymmetric in 60% of cases; all had negative tests for rheumatoid factor. Some of these patients have received steroids on a long-term basis with the usual side effects, including truncal obesity, susceptibility to infection, osteoporosis and moon facies. Total hip or knee replacement and synovectomies have been required. One patient was recently given a course of methotrexate and acceptable control of symptoms was subsequently achieved with lower doses of prednisone. The follow-up results indicate that in some persons with adult Still's disease, chronic arthritis develops that can be debilitating and resistant to therapy. Similar results have been reported in children with juvenile rheumatoid arthritis.[26,40-43]

Overview

Adult Still's disease has evolved into a well-characterized disease entity. This categorization allows physicians to place

a unifying label on the rare, puzzling case of a patient who presents with a systemic illness characterized by high spiking fever of unknown cause associated with intense arthralgias or arthritis; an evanescent, erythematous macular or maculopapular rash, and other less constant features of systemic illness, including lymphadenopathy, hepatosplenomegaly, sore throat, leukocytosis, anemia and increased concentration of hepatic enzymes. The diagnosis of adult Still's disease is based solely on compatible clinical findings; serologic or other diagnostic tests do not aid in diagnosis. The diagnostic problem presented by these patients with such severe systemic illness and the insecurities inherent in diagnosis based *solely* on clinical features make the availability of the diagnosis, adult Still's disease, useful in patient care.

The cause of adult Still's disease is unknown. Some have speculated that the disease has features of nonnecrotizing immune complex vasculitis.[28] Rubella infection has been associated with adult Still's disease,[44,45] but no definite etiologic relationship has been established. Neither rubella infection nor any other potential antigen has been identified consistently in association with the disease.

Managing patients with the disease depends on establishing the correct diagnosis. The diagnosis should include both recognition of the syndrome and exclusion of other possible diseases. Controlling systemic manifestations may require unusually high doses of aspirin, indomethacin or other nonsteroidal anti-inflammatory drugs, prednisone or combinations of these drugs. Some adults appear to require both high doses of prednisone and indomethacin to control disease manifestations. Fortunately, systemic attacks are usually episodic; steroid toxicity can be minimized by the use of alternate-day dosage and attempts to discontinue steroid use between episodes.

The experience with the University of Washington patients[10] and other reports of long-term follow-up[29,37] indicate that adult Still's disease may be more disabling than was originally reported. At least three patterns of recurrences occur: episodic systemic attacks with or without arthritis, episodic pauciarticular arthritis and disabling, deforming chronic arthritis that may require surgical intervention and long-term anti-inflammatory, gold or cytotoxic therapy.

Progress in adult Still's disease can occur on several fronts. Recognition and diagnosis can be more prompt and efficient; follow-up is often critical for an accurate diagnosis. Understanding the cause of the disease or diseases the syndrome represents is critical because current knowledge is largely descriptive. Finally, therapeutic advances are needed, especially for patients with chronic polyarthritis and its sequelae.

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Medical Staff Conference

Should Postmenopausal Women Be Given Estrogen?

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs Homer A. Boushey, Associate Professor of Medicine, and David G. Warnock, Associate Professor of Medicine, under the direction of Dr Lloyd H. Smith, Jr, Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143.

DR SMITH:* *Osteoporosis is a common and important problem in the elderly, especially in women. The relationship of osteoporosis to estrogen deficiency has been known for almost half a century, perhaps most clearly established in the work of the brilliant clinical investigator Fuller Albright. The implications of this association are still being debated, however. Is the postmenopausal state an endocrine deficiency syndrome that should be treated? When should estrogens be used to prevent the development of the fragile bones of osteoporosis and the resulting fractures leading to disability and, all too often, to death? Today we have asked Dr Richard J. Haber from the San Francisco General Hospital Medical Center to review this important topic for us.*

DR HABER:† Should all postmenopausal women be given estrogen? If not all, can subgroups of the population be identified who would benefit? Because there are currently more than 30 million women in the United States in the postmenopausal age group and because each woman can expect to live approximately a third of her life after menopause, this is an issue with public health implications. I will focus on three basic questions: Do certain phenomena occur during and after the menopause related to a decreased production of estrogen? Can these phenomena be prevented or reversed by estrogen administration? Do the benefits of estrogen therapy outweigh the risks?

Certain aspects of the menopause are relevant to our discussion. The menopause is characterized by decreased estrogen and increased gonadotropin secretion. Estrogen secretion continues after menopause but total production is reduced and the source, profile and cycle of secretion are different.[1] As ovarian production of estrogen ceases, conversion of adrenally produced androstenedione to estrone, primarily in fat tissue, becomes the primary source of estrogen. The amount of postmenopausal estrogen production varies and is directly related to body weight, an observation that may have implications for identifying women at different risk for conditions caused by estrogen deficiency. Because postmenopausal estrogen therapy does not restore gonadotropins or estrogens to premenopausal levels and does not recreate premenopausal hormonal profiles or cycle, the term estrogen "replacement" therapy is not accurate and will not be used.

Benefits

For purposes of discussion I will divide claims for postmenopausal estrogen therapy into perimenopausal and postmenopausal categories, recognizing that there is overlap between the two. I will focus primarily on indications for long-term estrogen therapy.

Proposed uses for estrogen therapy in the perimenopausal period have included relief of vasomotor (hot flashes), atrophic genitourinary and depressive symptoms and treatment of sexual dysfunction. There is convincing evidence that estrogen administration can relieve vasomotor and genitourinary symptoms and these constitute valid indications for at least short-term therapy. There is no persuasive evidence that estrogen therapy can relieve depressive symptoms or sexual dysfunction, except as these may be related to relief of vasomotor or genitourinary symptoms, and these problems cannot currently be considered indications for estrogen use.[1]

Proposed uses for estrogen therapy in the postmenopausal period have included the prevention and treatment of osteoporosis and coronary heart disease.

Osteoporosis

Because of an increase in bone resorption in excess of bone formation, there is a progressive loss of bone mass in the perimenopausal and postmenopausal periods. This loss is associated with a pronounced increase in fractures of the radius, hip and vertebral bodies, events much more frequent in women than in men.[2,3] Because rapid bone loss occurs in young women who have undergone premature surgical menopause, this phenomenon seems more closely related to meno-

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pausal status than age.[4] These observations suggest that estrogen deficiency may play a causal role in the development of postmenopausal osteoporosis and fractures and that estrogen therapy might prevent these events.

There are important racial differences in osteoporosis. The incidence of hip fracture in black women, possibly because of a greater premenopausal bone mass, is far less than that in white women and not different from that in white or black men.[5] This suggests that estrogen therapy would be of less benefit in black women than in whites in preventing fractures. Unfortunately, fracture rates in other racial and ethnic groups are virtually unknown. Available data suggest that white women who have undergone premature surgical menopause and thin women may be at greatest risk for osteoporotic fractures. Other factors that may identify those at higher risk include Northern European origin, a history of cigarette use, alcoholism and a sedentary life-style.

Does estrogen therapy prevent loss of bone mass? Multiple randomized and nonrandomized controlled trials have consistently shown significant preservation of bone mass in estrogen-treated women when compared with placebo or other non-estrogen-treated control groups.[2,3] Treatment is effective whether begun in the perimenopausal period or as late as age 70 and following natural or surgical menopause. Bone mass has been measured using a variety of methods at both appendicular (hand and forearm) and vertebral sites and bone mass preservation has been documented to persist during nine to ten years of continued therapy. Although an increase in bone mass has been reported in some studies, this phenomenon has not been consistently observed and substantial new bone formation is probably not a realistic expectation of estrogen therapy. Once lost, therefore, bone mass cannot be replaced and estrogen therapy should be thought of as prophylactic.

Does estrogen therapy prevent fractures? Osteopenia is not known to be a morbid condition except as it predisposes to fracture. Therefore, bone mass preservation would be of little practical value if fracture rates were not also decreased. Studies of the relationship between postmenopausal estrogen use and fractures of the hip and radius report risk in estrogen users to be about half that of nonusers. Similarly, studies of vertebral fractures consistently report estrogen is effective in primary and secondary prevention of these events.[2,3]

Osteoporotic fractures have significant clinical impact. The annual incidence of hip fractures in the United States in postmenopausal white women is about 500 per 100,000; a woman entering menopause has an approximately 15% chance of sustaining a hip fracture in her remaining lifetime. Although published estimates of the mortality associated with hip fracture vary widely, a conservative estimate of mortality attributable to the fracture is 10%.[6,7] The effect of hip fracture on quality of life in the elderly is as or more important than the associated mortality. About 40% of postmenopausal women sustaining a hip fracture do not return home, either dying or remaining in long-term-care facilities.

Coronary Heart Disease

Premenopausal women enjoy relative protection from coronary heart disease. Loss of this protection is more closely correlated with menopausal status than with age.[8] These observations have led to the hypothesis that the postmenopausal increase in coronary heart disease risk may be causally related to estrogen deficiency and that estrogen therapy might decrease this risk. Elevation ("worsening") of the ratio of low-density to high-density lipoproteins after menopause and lowering ("improvement") of this ratio by estrogen therapy provide a possible mechanism for this effect.

Does estrogen therapy, in fact, lower cardiovascular risk? Although a substantial portion of available evidence supports a protective role, the data are inconclusive and the issue must currently be regarded as unsettled. After adjustment for confounding risk factors, all retrospective case-control studies of estrogen therapy in women older than 50 years report the relative risk in estrogen users to be less than in nonusers.[9-12] Two other studies, using different designs, also note a protective effect.[13,14] Data from an eight-year portion of the Framingham study, however, indicate an increased risk of coronary heart disease in estrogen users, primarily due to a significantly increased risk of angina.[15] No significant increase in fatal or nonfatal myocardial infarction or overall mortality was observed. When smokers were excluded there was no longer a significant difference between estrogen users and nonusers for any category of coronary heart disease.

Knowledge of the relationship between postmenopausal estrogen therapy and coronary heart disease is critical to analyzing the relative benefits and risks of estrogen therapy. Because coronary heart disease is the leading cause of morbidity and mortality in postmenopausal women, even small alterations in risk could greatly affect the overall benefit:risk ratio. If risk were significantly decreased by estrogen therapy, then preventing coronary heart disease would become the major indication for long-term estrogen therapy. Conversely, any significant increase in risk could negate all known benefits. Alteration of coronary heart disease risk cannot currently be considered a proven "benefit" or "risk" of postmenopausal estrogen therapy, but remains an issue that urgently requires clarification.

Risks

Theoretically, all risks associated with the use of oral contraceptives could also be seen with postmenopausal estrogen therapy. In fact, a consistent relationship between postmenopausal estrogen therapy and thromboembolic, coronary heart, cerebrovascular, hypertensive or hepatic disease has not been observed. A twofold increase in cholelithiasis has been reported.[16] Why the effects of premenopausal and postmenopausal estrogen use might be different is unclear, but the lower postmenopausal dose, the estrogen-progestin combination in the oral contraceptives or differences in age could be responsible. Of greater worry has been that postmenopausal estrogen therapy might increase the risk of malignancy in estrogen-sensitive tissues such as endometrium and breast.

Endometrial Cancer

Although a randomized controlled trial is lacking, multiple lines of evidence strongly suggest that users of postmenopausal estrogen are at increased risk for endometrial cancer.[17,18] However, the magnitude of this risk is low and an adverse effect on survival from estrogen-associated tumors has not been found.

Estrogen users were initially reported to be at approxi-

mately fivefold greater risk than nonusers, but subsequent data suggest that relative risk in these studies may have been significantly overestimated.[19-21] Because endometrial cancer is an uncommon disease (annual incidence, 100 per 100,000 women), regardless of relative risk, the absolute risk to a woman is small. For example, even assuming a fivefold increase in risk, a woman's chance of estrogen-associated endometrial cancer developing is still less than 0.5% per year. Because risk is related to dose, the lower doses of estrogen currently used should be associated with an even lower risk than described in these earlier studies. To put this degree of risk in perspective, the risk of endometrial cancer associated with postmenopausal estrogen use is about the same as for women in the upper 15% to 20% of the population by weight.[22] Even more important, estrogen-associated endometrial cancer has been consistently characterized by diagnosis at an early stage, a high degree of differentiation and minimal myometrial invasion.[23,24] Survival is significantly better than with cases of non-estrogen-associated cancer and equal to[25] or significantly better than[26] the general population matched for age and race. The differences between estrogen-associated and non-estrogen-associated endometrial cancer could be due to earlier detection, a less aggressive natural history for estrogen-associated tumors or overdiagnosis. Whatever the explanation, estrogen-associated cancers do not appear to cause a decrease in life expectancy.

A comment about the use of progestins in the postmenopausal period is appropriate. Despite limited information as to efficacy and safety, it has recently become popular to add a progestin to the monthly estrogen regimen in an attempt to decrease the risk of endometrial cancer. Unfortunately, the long-term effects of the use of progestins in the postmenopausal period are virtually unknown. Progestins have adverse effects on lipid risk factors for coronary heart disease and all cause mortality and in combination with estrogens are pharmacologically similar to the oral contraceptives. Their use, therefore, may negate any beneficial effect of estrogen on cardiovascular and overall mortality and could result in a higher risk than in those using no hormonal therapy. In this context, the observation that when the estrogen dose is controlled for, the risk of cardiovascular and cerebrovascular disease in oral contraceptive users is directly related to progestin dose is of concern,[27] as is the possibility that the monthly bleeding induced by an estrogen-progestin regimen may be unacceptable to a substantial portion of women and result in discontinuation of all hormonal therapy. The risk of estrogen-associated endometrial cancer, an uncommon disease of uncertain clinical significance, may be diminished at the expense of the overall benefit:risk ratio for postmenopausal hormonal therapy. Until these issues are clarified, I believe that the widespread use of progestins in the postmenopausal period is premature.

Breast Cancer

There is little convincing evidence that postmenopausal estrogen therapy alters the risk of breast cancer.[28,29] Unlike endometrial cancer, no relationship between breast cancer rates and postmenopausal estrogen consumption has been noted. Multiple retrospective case-control studies have shown the overall relative risk of breast cancer in estrogen users to be no greater than in nonusers, and no consistent relationship between risk and dose has been observed. In two differently designed studies, breast cancer rates were significantly lower in estrogen users than in actual or "expected" controls.[20,30] In three other studies no significant difference was observed.[13,21,31]

Subgroups of the population at higher risk for breast cancer with estrogen therapy have not been consistently identified. A prior history of breast cancer precludes estrogen therapy, as may a strong maternal family history of the disease. Risk beyond ten years' duration of therapy is poorly documented and deserves further study. Attention to routine breast cancer screening in women receiving postmenopausal estrogen therapy is important, although there is no evidence that screening must be more frequent or different from that recommended for the general population.

Benefits Versus Risks

In Table 1 changes in mortality rates attributable to postmenopausal estrogen therapy are compared. Gallbladder disease and perimenopausal symptoms have been omitted because they contribute relatively little to overall morbidity and mortality. The estimates used in the table are necessarily simplified and quality of life is not quantitatively addressed. The proportion of morbidity and mortality attributable to hip fracture per se, as opposed to other concomitant medical problems, remains unclear, as does the morbidity attributable to vertebral fractures (not included in the analysis). Additionally, the clinical impact from hip fracture may occur later in life than that from estrogen-associated endometrial cancer. On the other hand, no adverse effect on survival from estrogen-associated endometrial cancer has actually been found.

TABLE 1.—*Changes in Risk Attributable to Postmenopausal Estrogen Therapy*

Benefits	*Annual Rate (Per 100,000)*	*Risks*	*Annual Rate (Per 100,000)*
Overall incidence, hip fracture	500	Overall incidence, endometrial cancer . .	100
Decrease in incidence attributable to estrogen therapy (½) (500-250=250)	(−)250	Increase in incidence attributable to estrogen therapy (3×) . . . . . (300-100+200)	(+)200
Mortality (10%) . . .	(−) 25	Mortality (5%)	(+) 10
Morbidity (40% do not return home)			
Incidence of coronary heart disease 1,000 Mortality 500			

Incidence and mortality rates for coronary heart disease are included to emphasize that even small changes in risk could significantly influence the benefit:risk ratio. For example, a 10% alteration in mortality from coronary heart disease would outweigh the combined mortality attributable to hip fracture and endometrial cancer. Perhaps the greatest value of this table is to emphasize that, taken in context, cancer does not always result in unacceptable morbidity and mortality and that fractures are not always benign. A postmenopausal white woman appears to be at a greater risk of dying of a hip fracture than of estrogen-associated endometrial cancer.

The all-cause mortality rate (survival) provides another means of assessing overall benefits and risks using a well-defined end point with obvious clinical significance. A therapeutic strategy that resulted in a significant increase in overall mortality would be difficult to recommend. Conversely, an increase in survival would be strong evidence that the net effect of therapy is favorable. Three nonrandomized prospective studies address the effect of postmenopausal estrogen therapy on the all-cause mortality rate.[13,15,32] In all, mortality rates in estrogen users were equal to or significantly lower than in nonusers. A survival advantage remained even in women who had not undergone hysterectomy and who were therefore at risk for endometrial cancer. In one study the negative association of estrogen use and mortality persisted after adjustment for age, smoking history, body mass, alcohol intake, education, systolic blood pressure and low-density-lipoprotein (LDL) cholesterol but was diminished when adjusted for high-density-lipoprotein (HDL) cholesterol. This suggests that some of the beneficial effects on mortality may be due to the increase in HDL-cholesterol levels in estrogen users, an observation that has implications for the use of progestins or any therapy that reverses the estrogen-induced rise in HDL cholesterol. These studies provide further evidence that postmenopausal estrogen therapy results in a favorable overall benefit:risk ratio even in those at risk for endometrial cancer.

Recommendations

Figure 1 is an algorithm designed to help structure the decision-making process as to which postmenopausal women should be given estrogen. This, like other therapeutic decisions, should be a mutual one—decided on by patient and provider and incorporating current medical knowledge and patient preferences.

If debilitating vasomotor or genitourinary symptoms are

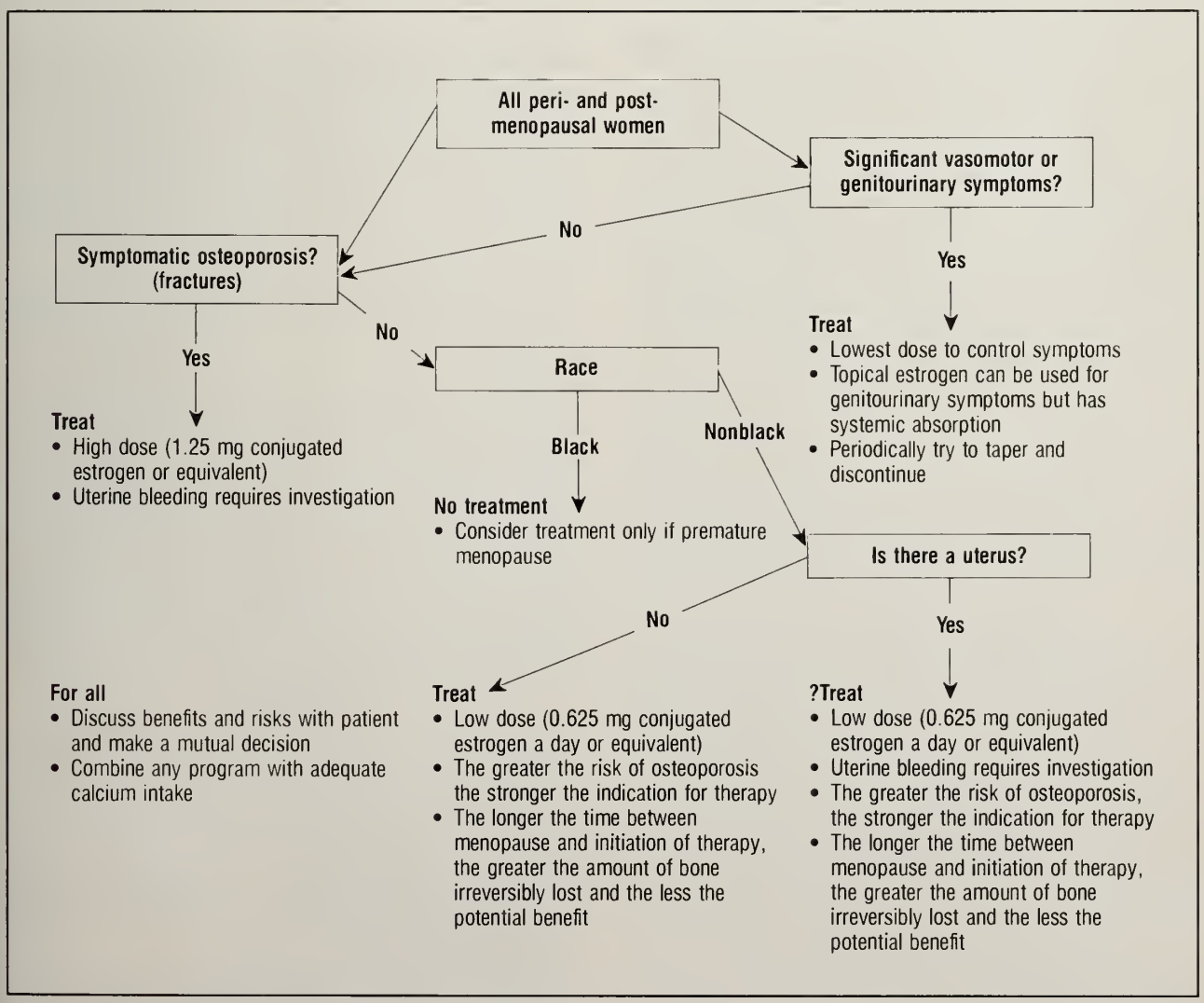
All peri- and post-menopausal women
Significant vasomotor or genitourinary symptoms?
No
Yes
Symptomatic osteoporosis? (fractures)
No
Yes
Race
Black
Nonblack
Treat
• High dose (1.25 mg conjugated estrogen or equivalent)
• Uterine bleeding requires investigation
Treat
• Lowest dose to control symptoms
• Topical estrogen can be used for genitourinary symptoms but has systemic absorption
• Periodically try to taper and discontinue
No treatment
• Consider treatment only if premature menopause
Is there a uterus?
No
Yes
For all
• Discuss benefits and risks with patient and make a mutual decision
• Combine any program with adequate calcium intake
Treat
• Low dose (0.625 mg conjugated estrogen a day or equivalent)
• The greater the risk of osteoporosis the stronger the indication for therapy
• The longer the time between menopause and initiation of therapy, the greater the amount of bone irreversibly lost and the less the potential benefit
?Treat
• Low dose (0.625 mg conjugated estrogen a day or equivalent)
• Uterine bleeding requires investigation
• The greater the risk of osteoporosis, the stronger the indication for therapy
• The longer the time between menopause and initiation of therapy, the greater the amount of bone irreversibly lost and the less the potential benefit

Figure 1.—Algorithm for the use of estrogen therapy in perimenopausal and postmenopausal women.

present, then treatment with the lowest dose of estrogen that will control the symptoms is indicated. Vasomotor symptoms, in particular, are self-limited and therefore should not be regarded as indications for long-term therapy. Because abrupt withdrawal can cause symptoms to recur, estrogen therapy should be tapered before discontinuation and the woman warned about the possible recurrence of symptoms. Although vaginal application of estrogen is effective for the relief of genitourinary symptoms, this route of administration also results in significant systemic absorption.

If postmenopausal osteoporosis has resulted in symptomatic vertebral fractures, then estrogen therapy is indicated to decrease further morbidity. Higher doses (1.25 mg of conjugated estrogens or equivalent) than for primary prevention may be required. For women who have not sustained osteoporotic fractures the major goal of long-term estrogen therapy is their prevention. Because the risk of osteoporotic fractures in blacks is low, it is difficult to recommend treatment except perhaps in those who have undergone premature surgical menopause. If postmenopausal estrogen therapy is proved to alter coronary heart disease risk or subgroups of black women at greater risk for osteoporosis are identified, then this racial differentiation will need to be reevaluated. Approximately 30% of women in the postmenopausal age period have undergone hysterectomy. Because such women are no longer at risk for endometrial cancer, the relative indication for estrogen therapy is stronger. The most problematic group is that majority of women who have not undergone hysterectomy and who are at risk for endometrial cancer. I believe it reasonable to treat such women if they are at risk for osteoporosis. Primary prevention of bone mass appears to require 0.625 mg of conjugated estrogens (or 25 μg of mestranol or ethinyl estradiol) per day. If an initial report that the estrogen dose can be further lowered (0.3 mg of conjugated estrogens) when combined with high-dose calcium supplementation (1,500 mg elemental calcium) is confirmed, then cancer risk may be further reduced without sacrificing bone preservation.[33]

My preference is to prescribe estrogen for 25 days each month even in women who have undergone hysterectomy. I believe it is prudent to combine estrogen therapy with adequate calcium intake (at least 1,000 mg of elemental calcium per day). I do not routinely add a progestin to this regimen. Ideally, therapy should be begun at the time of the menopause because the longer the time between menopause and initiation of therapy, the greater the amount of bone mass irretrievably lost.

For women unwilling or unable to use estrogens, there are no demonstrated therapeutic strategies that have equivalent bone-preserving properties. Supplemental calcium therapy seems the best alternative although studies have not always shown it to be better than placebo. Because postmenopausal women require a higher daily calcium intake than premenopausal women or postmenopausal women using estrogen,[34] the sum of dietary and supplemental calcium should be 1,500 mg of elemental calcium per day if estrogen therapy is omitted. Although fluoride, calcitonin and vitamin D and its active metabolites may have a role in the secondary prevention of vertebral fractures or in primary prevention when estrogen therapy is not used, such therapy is of unproved value, is associated with complications and should currently be regarded as experimental.

There are many important questions with regard to postmenopausal estrogen therapy that remain unanswered. Prominent among these are (1) Who is at greatest risk for osteoporotic fractures and how can they be prospectively identified? (2) What is the optimal hormonal regimen for those at risk? (3) What is the relationship between postmenopausal estrogen therapy, coronary heart disease and all-cause mortality?

Questions and Answers

PHYSICIAN IN THE AUDIENCE: *If you elect to implement estrogen therapy, can you elaborate on the duration of therapy?*

DR HABER: The optimal duration of estrogen therapy is unclear. Estrogen therapy is effective in preventing loss of bone mass during at least ten years of continuous therapy. Because there may be accelerated bone loss when estrogen therapy is discontinued and fracture protection may be lost as early as five years after stopping therapy, the ideal duration of therapy may be lifelong.

PHYSICIAN IN THE AUDIENCE: *Do you see any role for measurements of bone mass in deciding whom to treat with estrogen?*

DR HABER: It would be advantageous to be able to prospectively identify those women who will suffer osteoporotic fractures, in order to direct treatment to those at greatest risk. Although the technology to noninvasively measure bone mass is currently available, the ability of such measurements to identify those who will subsequently have fractures has not yet been shown. Until their predictive ability is validated, I believe the use of such tests, outside of a clinical research setting, is premature.

PHYSICIAN IN THE AUDIENCE: *Should one initiate estrogen therapy in asymptomatic women already 20 or 30 years postmenopause?*

DR HABER: I do not routinely begin estrogen therapy in such women. The rate of bone loss appears to be most rapid in the perimenopausal period, slows to about 1% per year in the next decade and seems to decrease even further in the very elderly. Although estrogen is effective in decreasing bone loss even when initiated as late as age 70, most bone loss will have already occurred by this age. The possible benefits of therapy, therefore, will be less, whereas the possible risks may not be proportionately reduced. Strategies aimed at preventing falls may be more productive for women in this age group, already at risk for fractures because of low bone mass.

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Epitomes

Important Advances in Clinical Medicine

Psychiatry

The Scientific Board of the California Medical Association presents the following inventory of items of progress in psychiatry. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, research workers or scholars to stay abreast of these items of progress in psychiatry that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Psychiatry of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to Division of Scientific and Educational Activities, California Medical Association, 44 Gough Street, San Francisco, CA 94103

Light, Season and Affective Disorders

ANIMALS LIVING within temperate zones deal with dramatic changes in the amount of light they receive during different seasons. One of the most obvious physiologic manifestations of seasonality is the phenomenon of seasonal breeding. It is now well established that the pineal gland hormone, melatonin, mediates the antireproductive effects of decreased light exposure during winter months. Annual rhythms in humans have also been established, including, for example, seasonal variations in suicides, general mortality, a need for electroconvulsive therapy and the incidence of episodes of depression and mania.

Recently, a group of patients suffering from "seasonal affective disorder" has been described. These 29 patients had a generally "retarded" type of depression, beginning in late fall or early winter with increased sleep, appetite and carbohydrate craving. They often would "fly south" for winter vacations, at which time they would note spontaneous remissions of their depression. They often had episodes of hypomania during spring and summer. Speculating that the decreased duration of light in the winter somehow had triggered the depressive episodes (comparable, perhaps, to a human form of hibernation), the investigators treated 11 of these patients by extending their photoperiod to a more "springlike" condition for two weeks. Light was full spectrum and 10 to 20 times brighter than normal room light, but 1/40th as bright as bright daylight. It was deemed "biologically active" by virtue of its ability to suppress pineal melatonin production. Preliminary data indicated a significant antidepressant response in all patients, which, however, was often followed by a relapse within several days after light treatment was stopped.

Treatment of depression with light must remain experimental until well designed, positive replication studies are done. Further work then might show what demographic, clinical and circadian rhythm characteristics would most likely predict responsiveness to light therapy, and, particularly, how to use this new technique most effectively.

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Attention-Deficit Disorder in Children—Diagnosis and Treatment

THE attention-deficit disorder with hyperactivity (ADDH) syndrome is one of the most common psychiatric problems in childhood. A diagnosis is most effectively attained by using systematic interviews with parents and children (such as the Diagnostic Interview for Children and Adolescents—a structured psychiatric interview), combined with rating scales completed by parents and teachers (such as the Conners).

The earliest view of the natural history of this syndrome was that children "outgrew" their problems by adolescence. An extension of this view is that treatment with stimulant medication should stop at the time of puberty because it would have a "stimulating" rather than a "calming" effect. Current research indicates that both of these views are wrong.

Prospective, retrospective and catch-up prospective studies of cases of the ADDH syndrome reveal the following. About half of the children are functioning relatively well in adolescence and adult life. The remainder have continuing symptoms and qualify for a diagnosis of ADDH residual

state. In addition, a substantial number of children with the disorder have significant problems as adolescents, with educational retardation and antisocial behavior, including substance abuse. Serious antisocial behavior is present in 10% to 50% of different samples of children with the ADDH syndrome when they reach adolescence. Almost all of these children who have significant substance abuse manifest other forms of antisocial behavior, and almost all of those children with the syndrome who show antisocial behavior in adolescence have ADDH residual state.

These findings are also true of adult samples. In addition, several studies have found high rates of "dysphoric disorders" in adults with the ADDH syndrome.

Psychopharmacologic studies of both adolescents and adults with ADDH indicate that stimulant medication is still effective and does not produce a "stimulating" effect. Sustained attention, impulsivity and motor activity are symptoms most affected by stimulants. Results of relatively long-term multimodality treatment studies suggest that multimodality intervention is quite effective in childhood. However, there is little evidence from published studies that treatment *limited to* childhood has any long-term effect in adolescence or adulthood.

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Hormones and Behavior

IT IS NOW well established that behavior influences hormone secretion and, conversely, that altered circulating hormone concentrations can influence behavior.

Altered secretion patterns of many of these hormones have been identified in cases of acute and chronic stress, in psychiatric illnesses including mania, depression and schizophrenia and as a result of drugs that act on the central nervous system—such as neuroleptics, alcohol and opiates. Perhaps most relevant to clinical psychiatry is the use of these hormone changes as tests to aid in the differential diagnosis of certain illnesses and to follow response to treatment. The dexamethasone-suppression test (DST) is the best known of these, having been proposed as a laboratory aid in the diagnosis of endogenous or melancholic depression, the subtype of major depression often requiring somatic treatment (antidepressants, electroconvulsive therapy). In the DST, the synthetic glucocorticoid dexamethasone, usually 1 mg, is given orally about midnight and the serum cortisol concentration is measured at certain times the next day. Dexamethasone normally suppresses adrenocorticotropic hormone and cortisol secretion for a full 24 hours, whereas 30% to 60% of patients with endogenous depression show an early cortisol escape, most likely on the basis of increased hypothalamic driving of the anterior pituitary-adrenal cortex. The practical application of the DST as a diagnostic aid has been hampered by issues of varying sensitivity (percentage of index cases with abnormal—that is, true-positive—DST results) and specificity (percentage of comparison cases with normal—that is, true-negative—DST results) and interference in the test results by a number of drugs and medical conditions. At present, the DST appears to be most useful in following the adequacy of treatment. Those patients with an abnormal pretreatment DST response who improve symptomatically with treatment but continue to have an abnormal test result are at greater risk for relapse than those patients whose DST findings revert to normal. The former patients may require electroconvulsive therapy in addition to pharmacotherapy for a full remission. In some patients with recurrent depression, the DST findings may again become abnormal several weeks before a clinically evident relapse. This is a promising aspect of the test that requires further study.

Similar limitations apply to another widely used neuroendocrine test for endogenous depression, the thyrotropin-releasing hormone (TRH) stimulation test, in which TRH is given intravenously and the serum thyrotropin (thyroid-stimulating hormone) level is measured. A thyrotropin response below a certain criterion level is considered blunted and thus abnormal. At best, both the DST and the TRH test should be applied only in selected cases and with full cognizance of their limitations both generally and in specific patients. They are neither screening tests nor substitutes for a careful clinical assessment.

Triiodothyronine, or T_3, the metabolically active thyroid hormone, may be a useful therapeutic adjunct to tricyclic antidepressants in some endogenously depressed patients who are refractory to the latter medications alone, even though such patients do not have clinically evident hypothyroidism. Presumably, the T_3 sensitizes postsynaptic neurotransmitter receptors in the central nervous system, similar to the mechanism proposed for the adjunctive effect of lithium in persons with tricyclic-resistant depression.

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Positron Emission Tomography in Psychiatric Disorders

POSITRON EMISSION TOMOGRAPHY (PET) is a new computerized tomographic technique that allows the visualization of brain structures relative to their uptake of radioactive tracers. Tracer substances are manufactured that contain unstable atoms which decay to emit a positron. This positron in turn annihilates with an electron to produce gamma particles. This radiation is picked up by sensors and a computer program is used to reconstruct a picture based not on x-ray density but on the local concentration of the tracer. PET scans thus permit us

to examine the biochemical functions of the brain in which the various positron-labeled tracer substances are involved.

The PET scan presently is strictly a research tool, though it may have applications in clinical psychiatry in the future. To date most studies have involved substances like water ^{15}O to look at blood flow or fluorodeoxyglucose ^{18}F to look at glucose metabolism. A few studies have been done using labeled drugs, most notably spiroperidol, which binds to and thus allows localization of dopamine receptors.

PET studies of glucose metabolism are already yielding interesting findings in cases of major psychiatric illness. In patients with chronic schizophrenia, glucose metabolism in the frontal lobes appears low when compared with that of posterior brain regions. This pattern is the reverse of that seen in normal persons. In mood disorders one group reports that patients with bipolar (manic-depressive) depression have low metabolic rates in all supratentorial brain structures when compared with normal persons, patients with bipolar depression who are in a manic state and even those with unipolar depression. In contrast, patients with unipolar depression show a decrease in the metabolic rate of the caudate nucleus relative to that of the person's brain as a whole. In another study, using water ^{15}O to study blood flow, those patients with panic disorder in whom an infusion of sodium lactate causes a panic attack were shown to have a decrease in blood flow to the left hippocampal gyrus compared with that on the right. These two interesting studies await replication.

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Use of Carbamazepine in Mood Disorders

CARBAMAZEPINE (TEGRETOL) is used extensively to treat partial complex (psychomotor or temporal lobe) and major motor (grand mal) seizures. In the past few years, carbamazepine has been shown to have value in treating cases of bipolar (manic-depressive) disorders. In studies carried out first in Japan and then in this country this drug has been remarkably effective both in treating patients with manic episodes and for maintenance to prevent recurrences. Its efficacy is on a par with that of lithium carbonate and many patients who do not respond to or cannot tolerate lithium can be effectively treated with carbamazepine. At present, it is usually only used in such patients. Carbamazepine may be effective in treating patients with depression, both bipolar and unipolar, though this is less well documented than its effects in cases of mania.

Treatment begins with 100 or 200 mg given twice a day, which increases, as patient tolerance permits, to a total of 600 to 1,600 mg a day (average dose about 1,000 mg a day). Carbamazepine blood concentrations do not correlate with therapeutic response in bipolar illness. Carbamazepine is compatible with most other psychiatric drugs. Some patients have required treatment with both carbamazepine and lithium to get an adequate response, though there are reports of occasional central neurotoxicity.

Carbamazepine is closely related to the tricyclic antidepressants and should not be added to the regimen of a patient already taking a monoamine-oxidase inhibitor. As with other tricyclics, monoamine-oxidase inhibitors can be added once a person is taking carbamazepine.

Many physicians have been unduly frightened about carbamazepine because of early reports of aplastic anemia occurring. Most of these cases were in elderly patients with numerous medical problems being treated with many drugs. Despite the increasing use of carbamazepine by neurologists and psychiatrists, there has not been a corresponding increase in cases of aplastic anemia related to its use. Side effects with the use of carbamazepine consist of those that can be seen with tricyclic antidepressants, but, in addition, there seems to be an increased incidence of dizziness (often true vertigo), pruritic rash and a mild lowering of the leukocyte count. Liver toxicity rarely occurs.

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Update on Electroconvulsive Therapy

ELECTROCONVULSIVE THERAPY remains a viable and important treatment in psychiatry. In California, for example, some 2,600 patients receive it each year (in spite of the strict legal requirements in the state).

More than a dozen different antidepressants are available in the United States, yet many patients with major depression respond only to electroconvulsive treatment. Response rates in the order of 70% to 90% have been shown. In some cases of severe life-threatening depression or in patients who are severely ill medically, electroconvulsive therapy is the treatment of choice. Manic patients who are not responsive to conventional treatments have about a 90% response rate to this treatment. Although manic exhaustion and depressive inanition were once common causes of death, today they are quite rare. Schizophrenic patients in acute stages who are unresponsive to standard treatments or who have experienced severe side effects, such as agranulocytosis or severe tardive dyskinesia, have a 75% response rate with electroconvulsive therapy. It is extremely safe, with a mortality rate of only 0.2 deaths per 10,000 treatments in California from 1977 to 1983.

There are virtually no absolute medical contraindications to electroconvulsive therapy. Although a brain tumor or a recent myocardial infarction are generally considered contra-

indications, it has been successfully given to patients with such a condition when absolutely essential for the patient. The most common side effects are (muscle contraction) headache and transient memory difficulty.

With premedication, anesthesia and hyperoxygenation, patients feel nothing and are often surprised, on awakening, to find that the treatment is completed.

New equipment using brief pulse stimuli allows a patient to receive less electrical energy than from a standard sine wave apparatus. Unilateral electrode placement is an option available to further lessen the transient memory disturbance that follows electroconvulsive therapy. However, not all patients who respond to this treatment will respond to unilateral treatment. The presence of a cerebral (not peripheral) seizure is necessary for a therapeutic response. Seizures can now effectively be monitored using electroencephalography to ensure that a therapeutic treatment is given. The expanded use of multiple monitored electroconvulsive therapy is being explored. This involves inducing three to five seizures in one treatment session in an attempt to effect a more rapid therapeutic response with fewer anesthesia inductions.

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The Behavioral Treatment of Obesity

Obesity is a major health problem in the United States. Public health statistics indicate that approximately 11 million men in the United States (19%) are obese; 18 million women (28%) are obese. For both men and women, the percentage increases with age. The mortality and morbidity of every disease are increased by the concurrent presence of obesity. Lowered self-esteem and a lifelong pattern of fighting negative cultural stereotypes are prevalent in obese persons.

Many studies have shown that obesity can be treated by modifying the antecedents to eating behaviors—that is, by changing responses to overt and covert stimuli, patterns of self-instruction and attributions to internal food cues and by decreasing cue salience. Eating behaviors can be changed through contingency contracting, social reinforcement, group approval and self-reward. Patients can be taught to change their eating habits by dietary and behavioral instructions—for example, by eating more slowly, eating in one place and emulating the food choices and eating style of their thin friends. Although not an eating behavior, exercise or an increase in physical activity is important in any weight-loss or weight-maintenance program.

Widespread replications have shown these techniques to be effective. Patients lose about ½ kg (1 lb) per week in behavior-modification programs for obesity. Stunkard showed that initially this effect can be enhanced by the use of appetite-suppressing medication; however, patients who received only behavioral-modification instruction have significantly better weight-loss maintenance than their matched peers in traditional counseling or drug-assisted therapies.

For patients who are as much as 40% overweight, current clinical practice is a dietary prescription of 750 to 1,200 calories with behavior-modification techniques for losing weight and maintaining weight loss. For those with more weight to lose, more aggressive therapies are necessary. For moderately obese patients—40% to 100% overweight—a protein-sparing modified fast of 320 to 400 kcal followed by a behavioral treatment program for maintaining weight loss is probably most effective. For the morbidly obese—patients 100% or more overweight who are resistant to dietary counseling or a fasting program—the vertical banded gastroplasty operation is the treatment of choice.

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The Role of Transference in the Doctor-Patient Relationship

In its traditional usage, the concept of transference has described our tendency to bring perceptions and expectations to our current interpersonal interactions that derive from earlier experiences with significant figures in our lives, rather than to relate specifically on the basis of the realistic attributes and behaviors of the person with whom we are interacting. Originally devised specifically to help us understand otherwise puzzling aspects of the relationship of a patient to the therapist in the psychoanalytic therapeutic situation, the concept was soon broadened to include perceptions and expectations brought to all relationships with significant figures in our lives (the transferences of everyday life) and, of course, within that, to the perceptions and expectations brought by patients to their physicians, as healers, as authorities and as persons to whom we entrust our care and who can do us good or harm (all aspects of the doctor-patient relationship).

Recent developments in psychodynamic understanding have made more explicit what is now called (by Gill) the two-way (social) rather than the one-way (asocial) paradigm of the transference. The one-way (asocial) paradigm is the traditional view just outlined, that transferences represent distortions of the realities of the current interactions by perceptions and expectations that derive from the past and are imposed upon and thereby color our perceptions of the new relationship in the present. According to this concept, a patient imposes his or her often inappropriate perceptions and expectations derived from past experiences upon the neutral, objective physician. The therapist as the more objective party and better judge of what is realistic and appropriate can then help the patient to differentiate perceptions that are distorted from those that are realistic.

According to the two-way (social) paradigm, the transference is constructed out of the interaction of two people, each of whom tries to plausibly construe his or her experience of the other in the relationship. This construing of the relation-

ship depends on the actual behaviors, attitudes and interactions as they are perceived through the expectations that one brings from past experiences with similar people or similar situations. In this concept, both parties try to make plausible sense of their relationship, both influence the way the other perceives them and both are influenced by the other's actual behaviors and by expectations that derive from their own personal pasts. In this conception it is not immediately clear what is realistic and what is distorted and how much a patient's way of construing the relationship makes sense in terms of how the therapist's actual attitudes and behavior are reminded of or confirm perceptions and expectations that were originally grounded in the patient's earlier life experiences.

This newer conception of the transference entails in turn an altered handling of it. Rather than seeing transference manifestations, with their roots in past experiences, only in terms of their inappropriateness to the present relationship and therefore as unrealistic, a physician might now look first to the current interaction with a patient to see what in it might be plausibly construed by the patient as if it were the same as, or a repetition of, an earlier relationship pattern. This becomes then an additional avenue to understanding and to tactful handling and tactful behavioral alteration by a physician in interacting with patients.

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Indications for Monitoring Psychotherapeutic Drug Concentrations

THE MEASUREMENT of concentrations of psychotherapeutic drugs in serum has recently been introduced into the field of psychiatry. The clinical indications for these drug level measurements are still being developed but the following generalizations can be sifted out of the literature.

Lithium Ion

Lithium ion is readily determined in serum. The recommended therapeutic range of 0.8 to 1.4 mmol per liter may be valid only for cases of acute mania; maintenance levels of 0.4 mmol per liter may be sufficient. Optimal maintenance levels and schedules are subjects of much current investigation.

Tricyclic Antidepressants

Suggested optimal tricyclic antidepressant concentrations are 100 to 300 ng per ml (400 to 1,100 nmol per liter) for desipramine hydrochloride, 50 to 150 ng per ml (200 to 550 nmol per liter) for nortriptyline hydrochloride and 100 to 200 ng per ml (400 to 750 nmol per liter) for protriptyline hydrochloride. Some investigators have noted deterioration at concentrations greater than 150 ng per ml of nortriptyline. For the tertiary amines, the following tentative ranges have been proposed: imipramine hydrochloride plus desipramine, 150 to 300 ng per ml; amitriptyline hydrochloride plus nortriptyline, 150 to 300 ng per ml (nortriptyline and desipramine are formed metabolically from amitriptyline and imipramine, respectively).

The utility of measuring such concentrations is controversial but appears to be most useful in cases of poor treatment response. The drug concentrations can then be used to assess whether poor compliance (which may exceed 50%) or aberrant metabolism is present. The use of drug concentrations is advocated to avoid toxic effects in high-risk populations, such as cardiac patients or elderly persons. Beyond these indications, the use of blood concentrations of tricyclic antidepressants is not considered cost effective by most authors.

Neuroleptics

Neuroleptic drug monitoring is in its infancy. Haloperidol is the best studied drug. Available studies suggest that both excessively high or low levels of haloperidol are associated with a poor clinical outcome. Studies are in progress with thiothixene and fluphenazine hydrochloride. At present no indications for measuring antipsychotic drug activity have been developed.

Benzodiazepines

Although benzodiazepines can be readily assayed, there is little agreement on the interpretation of serum concentrations. A major problem is the heterogeneity of conditions treatable with these agents.

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Mass Hysteria

RECORDED IN THE medical literature for centuries, mass hysteria continues to perplex both clinician and researcher. Although recent studies have clarified the characteristic patterns of such epidemics, sudden outbreaks of illness routinely stir up controversy about whether they are physical or psychological in origin. With public alarm about environmental pollution increasing during the past decade, attempts to find toxic causes for these epidemics have intensified.

An estimated four to six separate outbreaks of hysteria reach public attention each year, but the actual incidence is unknown. Mass hysteria is defined as the occurrence in a group of people of a constellation of physical symptoms suggesting an organic illness but resulting from a psychological cause, with the typical epidemic affecting from 30 to several hundred people. The characteristic features of mass hysteria that help differentiate such epidemics from those due to physical causes include the absence of laboratory results and physical findings confirming a specific organic cause; a

preponderance of the illness in girls or women; the apparent transmission of illness by sight or sound, or both; the presence of hyperventilation or syncope; a preponderance of illness in adolescents or preadolescents; benign morbidity, often with rapid spread followed by rapid remission of symptoms; relapses of illness in the setting of the original outbreak; and evidence of unusual physical or psychological stress.

The usual question is how far to pursue various chemical tests without undertaking an endless search for an organic cause. No single toxicologic or epidemiologic finding is pathognomonic; sudden outbreaks of illness are sometimes found to have organic and psychological causes, and both possibilities should be explored initially. Intervention should also include dispersion of the group and discontinuation of extensive environmental and laboratory investigations once the characteristic pattern of hysteria emerges.

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Editorials

CME and the Pace of Change in Medicine and Society

THERE IS MUCH at stake for physicians and the medical profession in today's environment of technologic and social change. What was once the more or less inviolate territory of physicians is now being entered by other health professionals. What was a more or less simple doctor-patient relationship is more and more the turf of a variety of third parties that are now impinging upon this relationship, each with its own goals and expectations in patient care. Practicing physicians and the medical profession are beleaguered on many sides. Their strength is certainly not in their numbers nor in their economic power. They are outnumbered by nurses and many other health professionals, by lawyers and many other third parties in health care, and the economic power in health care is clearly in the hands of others. Where then is their strength? This must lie in their special knowledge, special skills and special expertise, and in the exercise of these in fulfillment of their responsibilities to society—that is, to benefit patients, the public and perhaps even the health and well being of humanity as a whole. If this is true, then this strength must not only be acquired by physicians, but maintained and exercised through a lifetime of practice in the face of rapid change in both medicine and the environment in which it is practiced. Nor should it be forgotten that knowledge can be power and that special knowledge can be special power.

The education of physicians is a complex subject. The formal education at the beginning, whether undergraduate in medical school or graduate in residency or fellowship training, is only preliminary to the continuing education and training that will be needed during a lifetime of practice. And this undergraduate and graduate training experience hardly prepares a physician to cope effectively with the pace of change in medicine and society that will lie ahead. A very present danger is that neither individual physicians nor the medical profession as a whole will be able to keep up sufficiently with the rapid changes that are and will be occurring, and this with predictable adverse effects on their responsibilities to patients and to society as a whole. To the extent that such failure occurs, not only leadership, but strength and power is lost.

Continuing medical education, or CME as it is commonly called, sits at the interface of changing science and changing practice, and as presently structured, it also does much too little to help physicians learn to cope efficiently with all the rapid change that is occurring. CME is not a simple educational process. It shares the problems of information overload with undergraduate and graduate education in medicine, and it needs to deal more specifically with the identified needs of each physician in his or her individual personal practice as well as the needs of the profession as a whole to deal with the health care needs of a relatively unchanging humanity in a rapidly changing human society. The time available to busy practitioners for CME is always limited and the time they do spend in this endeavor should be much more efficiently used than is now usually the case. All of this suggests that there should be some better preparation and better organization of most physicians' continuing education.

At the risk of very great oversimplification it would seem that at least four categories of more formal or structured CME are needed.

1. *CME to maintain professional competence in patient care.*

This should at least include keeping up with one's own specialty or subspecialty, maintaining some awareness of what is going on in other specialties (since one has to treat whole persons as well as their specialized parts), and some method of identifying educational or training needs to maintain professional competence in one's own ever differentiating practice.

2. *CME to maintain quality of care in the changing health care environment.*

This is needed to be effective patient care advocates and to cope effectively with the third parties that abound in the health care environment. Most physicians have little or no training to help them understand, let alone prevail in the rapidly changing social, economic and political whirlwind that is battering their patients, their profession and themselves. Some kind of CME seems greatly needed to develop greater professional competence in this area of practice.

3. *CME to promote health and the prevention of illness.*

This would deal with the responsibility of physicians and the profession to promote health and the prevention of illness in all their relationships with individual patients, families, communities, regions, states and even nations.

4. *CME to understand and use new and developing tools and resources for CME.*

This would relate to CME about CME itself, and particularly its new dimensions based on the use of computers, electronic access to stored information, new methods of information transfer, patient care data bases that can be used not only for cost control, but for quality control as well, and soon will be available for personal, professional and patient care accountability. The new tools and resources will be more efficient and more responsive to specified practice needs and will gradually displace many inefficient though time honored hospital, specialty society, medical school and entrepreneurial didactic programs from which a physician often gains relatively little for the time spent.

The future stature and status of physicians and the medical profession in society will no doubt greatly depend on how current and up to date they are able to keep their special knowledge, skills and expertise, and on how effectively they apply these in patient care and to the health related problems of an ever more complex and interdependent society. In this view CME emerges as a most important, yet much underrated, segment in the continuum of medical education. The organization and structure to do what needs to be done remain

to be defined. But there is much at stake in all of this for the future of the medical profession. If it is to play its proper role, the profession itself should earn recognition as "physician to society" in all matters pertaining to health and health care, in much the same sense that a doctor is recognized as physician to a patient, but it will surely take new concepts and better performance in CME to bring all this about.

MSMW

Radiocontrast Nephrotoxicity

Acute renal failure occurs frequently in the contemporary practice of medicine. Hou and collaborators studied prospectively 2,216 in-hospital patients and found that some degree of acute renal insufficiency developed in 4.9%.[1] The incidence of acute renal failure approaches 15% to 50% in selected clinical settings such as intensive care unit admission, serious trauma and burns, complicated open heart and abdominal aortic aneurysm operations and following aminoglycoside therapy.[2] Despite significant advances in the care of patients with acute renal failure and the ready availability of dialysis, current mortality rates are 15% to 25% for nonoliguric and 30% to 80% for oliguric acute renal failure.[3] The high frequency of occurrence and significant mortality of acute renal failure demand that attention be directed to preventive measures.

It is noteworthy that 15% to 25% of all cases of acute renal failure can be attributed to commonly used therapeutic agents.[2] Several factors underlie renal vulnerability to toxic injury. Normal renal function requires the interaction of both vascular and tubular elements and injury to either can lead to renal failure. The kidney receives 25% of the cardiac output and is exposed to high concentrations of blood-borne substances. The ability of the kidney to concentrate glomerular filtrate severalfold plus renal tubular transport processes exposes renal cells to even higher concentrations of potential toxins. Numerous enzymatic and metabolic pathways are operative within the kidney that may be particularly susceptible to nephrotoxic injury. Because of these factors, therapeutic agents such as immunosuppressants (cyclosporine), antimicrobials (aminoglycosides, amphotericin B), heavy metals (cisplatin) and anti-inflammatory drugs (nonsteroidals) are often implicated as causes of acute renal failure.[2]

In this issue of the journal, Misson and Cutler provide a comprehensive overview of acute renal failure following the diagnostic use of radiocontrast agents. Four "take-home" messages of this excellent review are as follows: (1) radiocontrast agents appear remarkably safe in healthy persons. In the presence of normal renal function, radiocontrast agents result in a less than 1% to 2% incidence of nephrotoxicity. (2) Patients with renal insufficiency (especially patients with diabetic nephropathy) are at high risk for radiocontrast nephrotoxic effects. A significant increment in serum creatinine concentration occurs in from 10% to 90% of azotemic patients. (3) Most patients with radiocontrast-associated acute renal failure experience a mild, transient increase in serum creatinine concentration. However, in 20% to 30% of patients, the increase in serum creatinine concentration is more pronounced or not reversible (or both). (4) The mechanism(s) underlying radiocontrast nephrotoxicity are unclear. Evidence supporting abnormalities of both renal vascular and tubular function is available.

Unfortunately, radiocontrast agents are often felt to be indicated in the assessment of patients at high risk for the development of acute renal failure. What is the best approach in such patients? Avoiding unnecessary contrast procedures is the first step. Other diagnostic procedures may provide the needed information. For example, excretory urography is often used to assess kidney size and the presence or absence of obstructive uropathy in patients with renal failure. Recent studies indicate that ultrasonography in experienced hands is a sensitive method for determining renal size and excluding obstructive uropathy.[4] Other preventive measures suggested by Misson and Cutler, such as avoiding volume depletion during preparation, avoiding the concomitant use of other nephrotoxins, using the smallest possible dose of contrast agent and maintaining a three-day interval between repetitive contrast exposures, are practical but unproven suggestions.

Are additional preventive measures indicated in a high-risk patient? No large prospective controlled studies are available to answer this question. However, retrospective studies suggest that administering 1.5 liters of a solution of 0.45% saline attenuates the effect of intravenous urography to elevate serum creatinine concentration in patients with chronic renal failure.[5,6] In addition, an uncontrolled prospective study of more than 500 patients suggests that a comparable or slightly greater degree of volume expansion results in a low frequency of acute renal failure following angiography even in high-risk patients.[7] Together, these observations support the recommendations of Misson and Cutler that until better data are available, patients with a serum creatinine concentration of more than 2 mg per dl (more than 1.5 mg per dl in cases of diabetic nephropathy) receive volume expansion (1.5 to 2.5 liters) before and during contrast exposure. What should be done in high-risk patients who are not suitable candidates for moderate volume expansion? A preliminary report of a prospective controlled trial of 27 patients suggests that 50 grams of mannitol in 180 ml of 5% dextrose solution given within 45 minutes of radiocontrast exposure attenuates the increment in serum creatinine.[8] Such therapy is usually well tolerated clinically. There are no clinical studies to support the proposed prophylactic use of potent diuretic agents, such as furosemide, in patients at high risk for radiocontrast nephrotoxicity.[9]

What does the future hold? Several laboratories are actively working on the pathophysiology of radiocontrast-associated acute renal failure in animal models. Such studies may lead to a more scientific approach to prophylactic therapy. As noted by Misson and Cutler, efforts are also under way to develop less nephrotoxic radiocontrast agents. Finally, newer visualization procedures which do not require radiocontrast exposure, such as nuclear magnetic resonance, may provide both physiologic and anatomic information. In the meantime, avoidance of unnecessary procedures and prophylactic therapy in high-risk patients appears to be the best course to follow.

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Health Care Dollars to Other Pockets

IT SEEMS REASONABLE to ask where all the health care profits are coming from and where they are going. There is considerable reason to believe that a large portion of these profits is the result of restrictions on those who provide and those who receive the services. The premise of the rhetoric we hear is that the profit motive will increase efficiency, reduce costs and eliminate the "fat"—and do all this without curtailing access or quality of care. The incentive for profit and the opportunity for competition is supposed to bring all this about, even in what may already be the most regulated health care system in the world.

There have always been profits in the health care field. The pharmaceutical industry has always done well and has had the incentives necessary to develop the wherewithal for much of the progress in patient care that has occurred. And some physicians have done very well indeed. Recently a growing number of hospitals and other health care institutions are being operated for profit. In the past, good hospitals, good skilled nursing facilities, good nursing homes and good home care agencies have not been considered very profitable operations. In fact, many, if not most, were operated "not for profit" and any "profits" were plowed back into the institution.

But now the health care system is being leached for dollars in ways it has seldom been, at least within recent memory. In the name of business efficiency, and to deal with the almost impossible complexities of government regulation, costly administrative hierarchies (with their accompanying organizational bureaucracies) are developing in hospitals and health care institutions that leach health care dollars for salaries and benefits for their ever-expanding management structures. The advertising, marketing and amenities stimulated by a growing competition for patients, pad the pocketbooks of many who actually contribute little if anything to health care. And the current orgy of malpractice and other litigation, so profitable to trial lawyers and others who thrive on litigation, adds new and often substantial costs to physicians' fees and the cost of a day's stay in hospital.

The public rhetoric continues to say—as it has for some time—that our goal is to have equal access for all to good quality medical care (although the *right* to care has been considerably muted), but that the cost of this has now become unacceptable. Yes, one may reasonably ask where all the profits in health care are coming from and where are they going. It is now becoming increasingly clear that in large measure they must be coming from restrictions on the providers of care and limitations on the options of patients who are the consumers of care, and both have had precious little to say about what is being done to them. One can only wonder if the goal should not be to get more of the needed health care from the admittedly scarce health care dollars, rather than to encourage all the competition, regulation and profiteering that divert so many needed health care dollars to other pockets.

MSMW

Adult Still's Disease—Implications of a New Syndrome

IN 1897 George Frederick Still felt it important to emphasize that the syndrome which came to bear his name be distinguished from rheumatoid arthritis in adults.[1] Almost 90 years later, we must decide if we should recognize an adult form of Still's disease as a separate nosologic entity. Citing the importance of the diagnostic, therapeutic and prognostic implications of recognizing a rare condition, several authors[2-4] have advocated the acceptance of the term adult Still's disease since it was coined by Bywaters in 1966.[5]

In this issue of the journal and elsewhere, Larson further supports this position by extensively reviewing the clinical features of the majority of reported cases of adult Still's disease and of 17 patients followed at the University of Washington.[4] In favor of recognizing adult Still's disease as a distinct syndrome is the remarkably consistent description of the clinical picture, with high fever, intense arthralgias or arthritis and a characteristic salmon-colored rash as prominent findings. Characteristically, the disease spares the metacarpophalangeal joints, a feature quite different from what is usually seen in rheumatoid arthritis. Standard serologic studies, such as antinuclear antibody and rheumatoid factor, are negative. An unusual ankylosing of the carpal bones occurs chronically; this is quite unlike more familiar rheumatic diseases, such as active rheumatoid arthritis in adults, mixed connective tissue disease or systemic lupus erythematosus.

But is this evidence enough? After all, it also is clear that the etiology is uncertain, no serologic tests are diagnostic[3] and, despite the existence of characteristic findings, in most cases the diagnosis is one of exclusion. Furthermore, probably because adult Still's disease is relatively rare, few longitudinal studies have been done. We are already learning that the disease is not as benign as once thought, with chronic arthritic changes developing in some patients. In view of this, can we be certain that patients with adult Still's disease will not eventually be found to be a subset of populations with another disease? This situation is reminiscent of what has occurred in mixed connective tissue disease where the diagnosis often rests mainly on a high titer of antiribonucleoprotein antibody. Some rheumatologists doubt the existence of mixed connective tissue disease as a distinct clinical entity; they point out that in a proportion of such patients followed for a decade or more, their disease appears to have evolved into typical systemic sclerosis or another connective tissue disorder.

Nonetheless, several standard sources of information, including *Harrison's Textbook of Medicine,* currently accept adult Still's disease as a separate disorder. The American Rheumatism Association also acknowledges its existence,[6]

although there are no defined criteria for the disease as there are with rheumatoid arthritis, systemic lupus erythematosus or systemic sclerosis.

One reason it is easy to accept adult Still's disease as a distinct syndrome is that by doing so we recognize several important clinical implications. The disease may be rare but the clinical presentation is not: 58% (11 out of 17) of the patients followed in Larson's series were being evaluated for fever of unknown origin and 70% (12 out of 17) had previous febrile episodes. Thus, the inclusion of adult Still's disease in the differential diagnosis of fever with a rash or fever of unknown etiology may significantly affect the cost and invasiveness of a given patient's workup.

Another advantage of accepting adult Still's disease as a clinical entity is that management may improve. Understanding the significant incidence of serositis[2] may positively guide evaluation of complaints which might otherwise go unheeded in a younger adult. An awareness of the frequently seen progression of carpal and tarsal arthritis might lead to earlier clinical and radiologic evaluation of these areas. Finally, there is the implication for therapy. Even though 60% of patients[4] with adult Still's disease may eventually require steroid therapy for disease control, recognizing the importance of salicylate trials in these patients might prevent excess steroid use with its attendant risk of morbidity.

The mysteries of this disease remain to be worked out. Is there a female preponderance as some have suggested,[4] and what role do hormones play in the etiology of the disease? Given the possible human leukocyte antigen associations reported,[3,7] what role do genetic factors play in the genesis of this process? If adult and juvenile Still's disease share the same cause, why is the syndrome rare in adults? In view of the 65% incidence of adenopathy in the current review, what relationship might there be between adult Still's disease and another controversial febrile illness—the adult mucocutaneous lymph node syndrome?[8,9] One day, adult Still's disease may join the list of diseases whose causes were previously unknown, such as toxic shock syndrome, Lyme arthritis and acquired immune deficiency syndrome. Until then, the recognition of this clinical entity may help in reducing the cost and morbidity often encountered in the evaluation and treatment of an undiagnosed febrile adult.

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Case Reports

Phenylpropanolamine and Cerebral Hemorrhage

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PHENYLPROPANOLAMINE HYDROCHLORIDE is a sympathomimetic drug, differing from amphetamine by only a hydroxyl group on the β-carbon atom.[1] It is a component of many decongestant and anorectic medications available without prescription.[2] Controversy regarding the safety of these substances centers about reports of adverse reactions, which include hypertension,[3-6] central nervous system stimulation,[1,7] renal failure[8] and cerebral hemorrhage.[9,10] Increasing concern over the significant side effects and abuse potential of phenylpropanolamine has prompted this report of three cases of cerebral hemorrhage in otherwise healthy women in whom no other cause could be found.

(McDowell JR, LeBlanc HJ: Phenylpropanolamine and cerebral hemorrhage. West J Med 1985 May; 142:688-691)

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Submitted April 11, 1984.

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Reports of Cases

Case 1

The patient, an 18-year-old woman, ingested eight "diet pills," each containing 50 mg of phenylpropanolamine and 200 mg of caffeine. Approximately two hours later she was seen in an emergency room with a blood pressure of 140/90 mm of mercury and a pulse of 52 per minute. Neurologic examination showed no abnormalities. She was given atropine sulfate and a gastric lavage. After discharge she had generalized convulsions and was brought back to the emergency room for admission. She was lethargic but awake and oriented without focal neurologic signs or symptoms. Her past history included normal results on a diagnostic evaluation for headache and obesity at age 12.

There was an abrupt deterioration of her mental state 24 hours after admission. Examination showed total loss of all brain-stem reflexes. Her spinal fluid was grossly bloody. Carotid angiography showed nonfilling of intracranial vessels and the electroencephalogram was isoelectric. Her condition did not improve and, after an appropriate interval, the patient was pronounced dead and respiratory support was withdrawn.

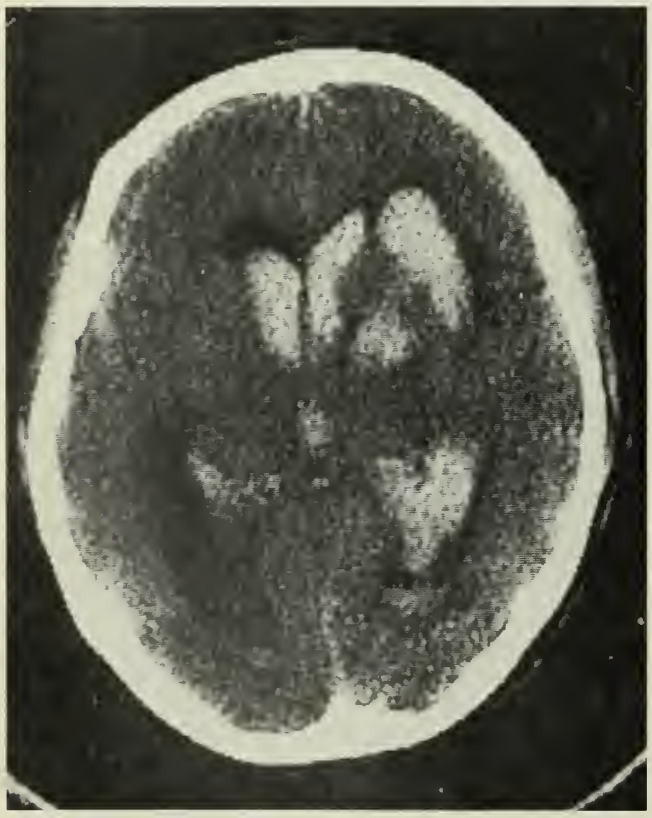

Figure 1.—Case 2. Computed tomographic scan showing intracerebral and intraventricular hemorrhage.

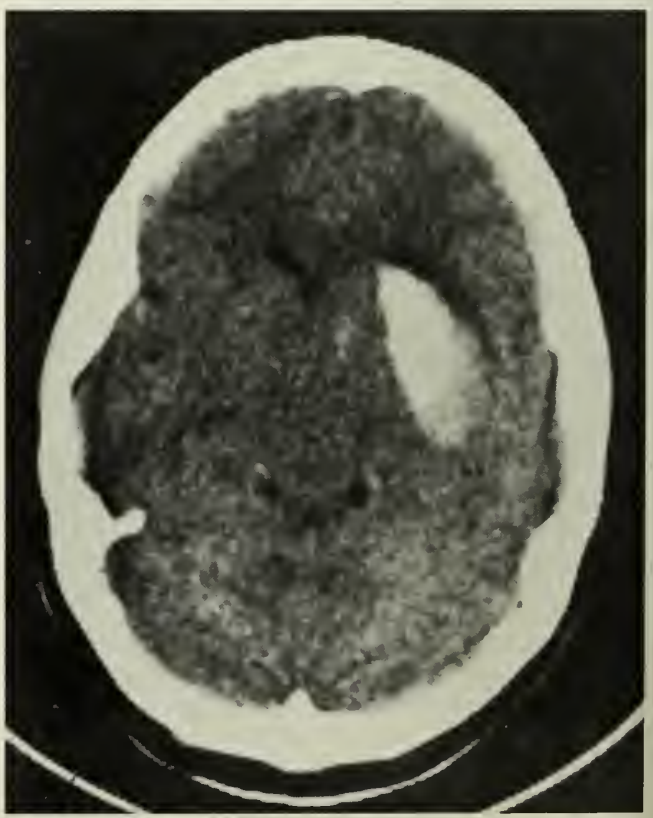

Figure 2.—Case 3. Computed tomographic scan done the day of admission showing deep left intracerebral hemorrhage.

Postmortem examination showed a right intracerebral hematoma with rupture into the lateral ventricle and subarachnoid space. There was diffuse brain swelling with tonsillar and transtentorial herniation. Detailed neuropathologic examination failed to identify a source of bleeding and microscopic examination showed no abnormalities of the cerebral arteries.

Case 2

A 45-year-old woman took a combination of aspirin and antacid for an upset stomach. Several hours later a headache and neck discomfort developed. She went to sleep and could not be aroused by her family two hours later. Paramedics were summoned who found her to be agitated but on arrival at the emergency department she was comatose with slowly reacting midposition pupils. She was breathing spontaneously with a blood pressure of 150 mm of mercury systolic. Her condition deteriorated rapidly over the next hour to apnea, anisocoria, then pupillary dilatation and unreactivity. She was hyperreflexic and decerebrate on the left side and soon lost all brainstem reflexes with ensuing apnea and flaccidity. A computed tomographic (CT) scan showed intracerebral and intraventricular hemorrhage (Figure 1). An electroencephalogram showed no activity of cerebral origin and, after an appropriate interval with no clinical change, the patient was pronounced dead.

The patient's previous health had been excellent. There was no history of smoking or hypertension. She had been taking phenelzine sulfate (Nardil), 15 mg three times a day, for chronic depression. The morning of her ictus she had taken for the first time two anorectic tablets, each containing 50 mg of phenylpropanolamine.

Postmortem examination showed a large right putaminal hemorrhage with extension into the globus pallidus and anterior horn of the right lateral ventricle. There was tonsillar and transtentorial herniation. Detailed neuropathologic examination failed to show a bleeding source and the cerebral arteries appeared normal on microscopic examination.

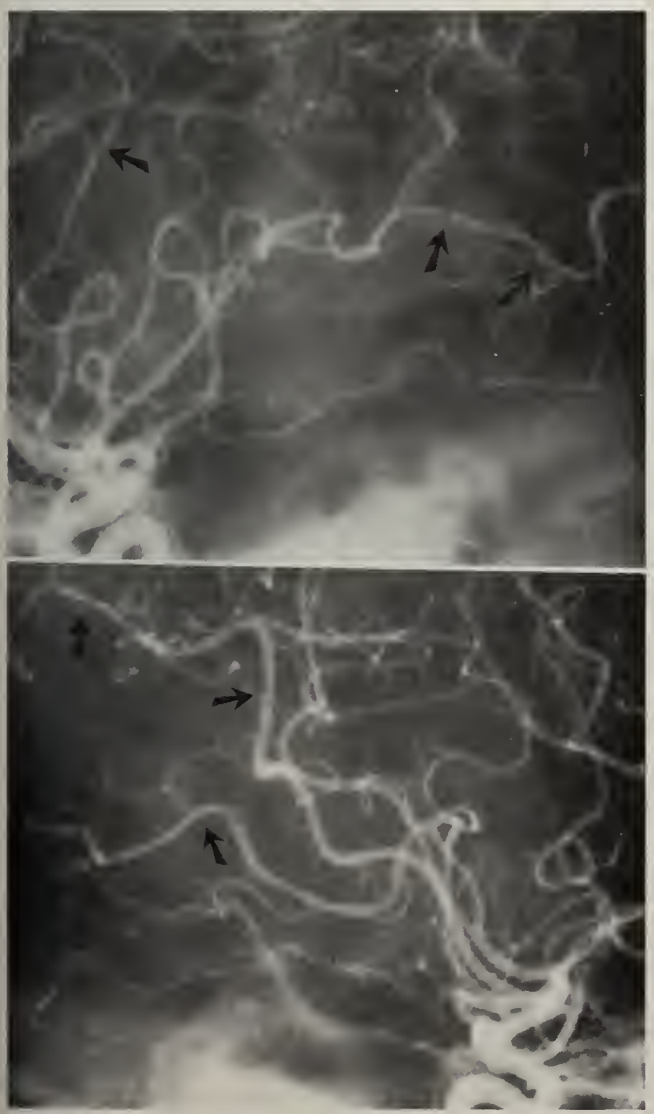

Figure 3.—Case 3. Carotid angiograms done shortly after admission showing segmental spasm (**arrows**) of distal branches of the middle cerebral artery. **Top,** Right carotid angiogram. **Bottom,** Left carotid angiogram.

Figure 4.—Case 3. Carotid angiograms done a month later with no further evidence of spasm. **Top,** Right carotid angiogram. **Bottom,** Left carotid angiogram.

Case 3

The patient, a 23-year-old woman, had a severe headache while driving home from work. Subsequently, her behavior became erratic and she was brought to the hospital where she was found to have right hemiparesis. She was otherwise in good health with no history of hypertension or drug abuse. A CT scan showed a deep left intracerebral hemorrhage (Figure 2). A retrograde femoral three-vessel cerebral angiogram showed no bleeding source, but there were areas of beading and irregularity of the diameters of several cerebral vessels (Figure 3).

Earlier that day she had taken two tablets of a proprietary "cold remedy," each containing acetaminophen, chlorpheniramine and 25 mg of phenylpropanolamine. Continued diagnostic evaluation included search for blood dyscrasia, collagen vascular disease, clotting disorder and evidence of latent or paroxysmal hypertension, but no abnormalities were found. The patient's course was one of pronounced improvement with only minimal hemiparesis and dysphasia detectable two weeks after onset. Repeat angiography one month later was normal (Figure 4), showing no bleeding source and interval clearing of the previously seen segmental narrowing.

Discussion

These three patients all had spontaneous intracerebral hemorrhages, two of which resulted in a fatal outcome. All three occurred in relatively healthy young women without an antecedent history of neurologic illness or hypertension. In the two fatal cases, a detailed postmortem examination of the brain failed to show a bleeding source such as aneurysm or arteriovenous malformation. The cerebral vessels were normal on microscopic examination. In one nonfatal case, angiography similarly failed to show a bleeding source but did show an irregularity of multiple cerebral vessels; this radiographic finding cleared completely with clinical recovery.

The temporal association of phenylpropanolamine ingestion and spontaneous intracerebral hemorrhage in these cases suggests a causal relationship. All three patients had taken drugs containing phenylpropanolamine the day of their hem-

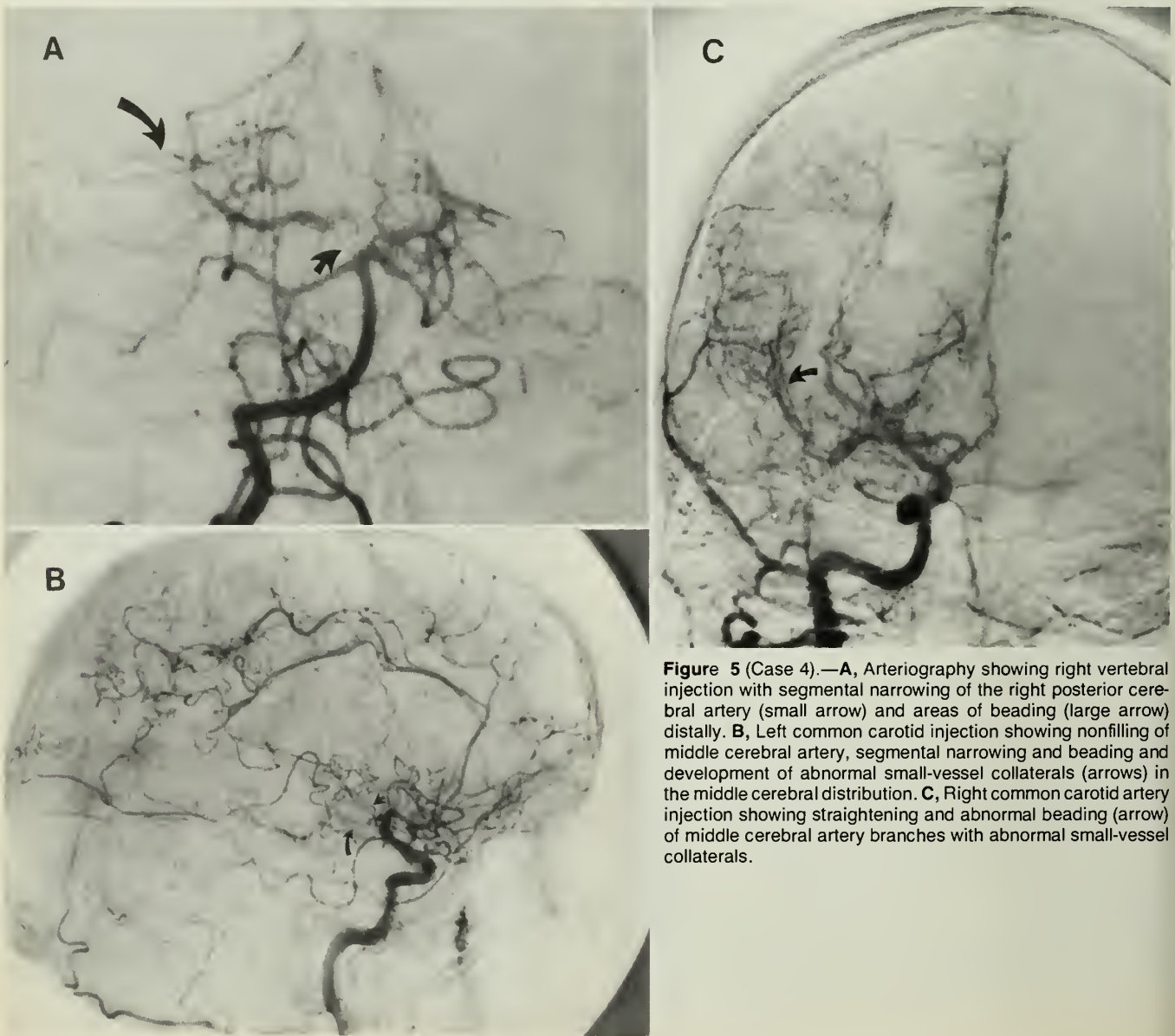

Figure 5 (Case 4).—**A,** Arteriography showing right vertebral injection with segmental narrowing of the right posterior cerebral artery (small arrow) and areas of beading (large arrow) distally. **B,** Left common carotid injection showing nonfilling of middle cerebral artery, segmental narrowing and beading and development of abnormal small-vessel collaterals (arrows) in the middle cerebral distribution. **C,** Right common carotid artery injection showing straightening and abnormal beading (arrow) of middle cerebral artery branches with abnormal small-vessel collaterals.

orrhage in amounts ranging from 50 to 400 mg. There were no signs of chronic hypertension found at autopsy of the two fatal cases, nor was there a history of hypertension in any of the three cases. No hypertension was noted on follow-up of case 3. Potentiation of the hypertensive sympathomimetic effect of phenylpropanolamine by a monoamine-oxidase inhibitor was a possible factor in case 2. Drug interactions between phenylpropanolamine and monoamine-oxidase inhibitors,[3] thioridazine hydrochloride[11] and indomethacin,[6] have been previously reported.

Hypertensive responses to phenylpropanolamine have been shown experimentally,[1] and hypertension has been part of the constellation of adverse reactions to phenylpropanolamine in clinical situations. Other prominent features have been headaches, seizures and changes in mental state.[7] Cerebral hemorrhage in association with phenylpropanolamine has been reported previously in only three cases.[9,10]

The angiographic picture in case 3 is similar to that previously described in association with amphetamine abuse and pseudoephedrine overdose,[12-14] both substances being chemically and pharmacologically similar to phenylpropanolamine. The reversal of these radiographic changes combined with the normal findings on pathologic examination of cerebral arteries in cases 1 and 2 suggests that the arterial change responsible for symptoms may be dynamic rather than anatomic, namely, spasm rather than arteriopathy.

Addendum

Since this paper was written, we have seen an additional very similar case.

Case 4

A 59-year-old woman had the abrupt onset of headache and nausea while eating lunch. Right hemiplegia rapidly developed and she became unresponsive. On examination, the patient was moderately overweight, had a blood pressure of 130/80 mm of mercury and frequent premature ventricular beats. She was mute but withdrew from painful stimulation. Brain-stem reflexes were intact and fundi were normal. A CT scan showed hemorrhage originating in the thalmus adjacent to the third ventricle with rupture into the ventricular system. Three-vessel arteriography showed multiple abnormalities in the intracranial vessels with segmental stenoses, beading and nonfilling of several branches (Figure 5). These changes were present in several areas, some quite distant from the site of hemorrhage. The patient's condition gradually improved and she was discharged to an extended care facility after three weeks in hospital. By that time, she could sit in a chair and was awake but mute, with a dense right hemianopia and right hemiplegia.

Ten years before admission to hospital, the patient had a right ventriculoperitoneal shunt because of the development of abnormal speech, gait and mentation. Before her acute illness, she was ambulatory and independent in the activities of daily living. She was a heavy smoker and was taking a "diet pill" daily containing 75 mg of phenylpropanolamine. Past medical history was otherwise unremarkable. She was found to have had an old diaphragmatic myocardial infarct and some chronic obstructive pulmonary disease.

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Septic Arthritis and Osteomyelitis of the Symphysis Pubis (Osteitis Pubis) From Intravenous Drug Use

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In four recently published series of infectious arthritis, synovial joints have typically been involved, usually in cases of prior joint damage from arthritis or trauma, joint replacement by prostheses, bacteremia from extraarticular infections with secondary hematogenous seeding of distant sites, prior use of immunosuppressive drugs or the presence of other debilitating conditions such as alcoholism, diabetes mellitus or malignant tumors.[1-4] Microbial organisms responsible for nongonococcal pyogenic arthritis in adults in these studies have most commonly been *Staphylococcus aureus* and other Gram-positive organisms and, much less commonly, Gram-negative or anaerobic organisms.[1-4] *Pseudomonas aeruginosa* was the responsible agent in only 12 of 218 patients reported in these combined series [1-4] and in only 1 of 12 cases of Gram-negative arthritis reported by Goldenberg and co-workers.[5]

Though these studies were from large metropolitan

(Magarian GJ, Reuler JB: Septic arthritis and osteomyelitis of the symphysis pubis (osteitis pubis) from intravenous drug use. West J Med 1985 May; 142:691-694)

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TABLE 1.—*Comparison of 13 Reported Cases of Pyogenic Osteitis Pubis in Parenteral Drug Abusers*

Case	Source	Duration of Symptoms	Temperature (°C)	Location of Pain	Drug Use	Leukocyte Count ($\times 10^3/\mu l$)	ESR (mm/h)	Hip Radiographs	Pubic Symphysis Radiographs	Radionuclide Scans	Site From Which Organism Cultured and Results	Histopathology
1	Magarian & Reuler	1 mo	37.2	Right thigh, both hips, suprapubic	Pentazocine, tripelennamine (Pyribenzamine) hydrochloride	10.3	52	Normal ×2	Normal	Positive pubic symphysis (1 mo)*	Aspirate-Pos, blood-Neg	ND
2	Sequeira et al, 1982[20]	7 wk	37.2	Hips, suprapubic	Pentazocine, tripelennamine	8.6	53	Normal	Initially normal; erosions and widening 2 wk later	ND	Aspirate-Pos, biopsy-Pos, blood-ND	Osteomyelitis
3	Sequeira et al, 1982[20]	1 mo	38.4	Left thigh, suprapubic	Pentazocine, tripelennamine	5.5	89	Normal	Erosive changes seen on initial radiographs	Positive pubic symphysis (1 mo)*	Aspirate-Pos, biopsy-Pos, blood-Neg	Osteomyelitis
4	Sequeira et al, 1982[20]	4 d	38.0	Bilateral inguinal, both hips, suprapubic	Pentazocine, tripelennamine	9.3	31	Normal	Initially normal; widening noted 10 d later	Normal pubic symphysis	Aspirate-Pos, blood-ND	Perichondritis
5	Sequeira et al, 1982[20]	2 d	37.4	Both hips, suprapubic	Pentazocine, tripelennamine	13.5	44	Normal	Periosteal reaction on initial radiograph	Positive pubic symphysis (2 d)*	Biopsy-Pos, blood-ND	Osteomyelitis
6	Del Busto et al, 1982[21]	1 wk	38-39	Left lower quadrant, left hip	Heroin	14.4	47	NR	Initially normal; widening and destruction 5 d later	ND	Aspirate-Pos, blood-Neg	NR
7	Del Busto et al, 1982[21]	4 d	Febrile temp NR	Right hip	Heroin	5.9	41	NR	Initially normal; widening and demineralization 15 d later	ND	Biopsy-ND, blood-Pos	NR
8	Del Busto et al, 1982[21]	1 wk	38.0	Suprapubic, right hip	Narcotics, Unspecified	9.6	NR	NR	Initially abnormal	Abnormal (9 d)*	Aspirate-Neg, biopsy-Pos, blood-Pos	NR
9	Del Busto et al, 1982[21]	4 wk	38.5	Suprapubic, left thigh and buttock	Narcotics, unspecified	9.6	85	NR	Initially abnormal	Abnormal (30 d)*	Aspirate-Pos, blood-Neg	NR
10	Del Busto et al, 1982[21]	8 wk	36.3	Left thigh, both inguinal regions	Narcotics, unspecified	4.0	95	NR	Initially abnormal	Abnormal (60 d)*	Aspirate-Pos, blood-Neg	NR
11	Del Busto et al, 1982[21]	4 wk	38.0	Suprapubic, both inguinal regions	Narcotics, unspecified	14.0	78	NR	Initially normal; abnormal 7 d later	Abnormal (35 d)*	Aspirate-Neg, biopsy-Pos; blood-Neg	NR
12	Kido et al, 1973[13]	4 wk	NR	NR	NR	NR	NR	NR	NR	NR	Aspirate-Neg, biopsy-Pos, blood-Neg	NR
13	Kido et al, 1973[13]	3 d	NR	Generalized skeletal pain	NR	NR	NR	NR	Destruction	ND	Aspirate-Pos, blood-Pos	NR

ESR=erythrocyte sedimentation rate, NR=not reported, ND=not done, Pos=positive, Neg=negative

*Duration from onset of symptoms.

teaching hospitals, the incidence of known parenteral drug abuse in such patients ranged from none of 59[1] to 19 of 54 patients.[3] Parenteral drug use predisposes to pyogenic infectious complications presumably from alterations in immune competence,[6] the injection of contaminated material or both. Staphylococcal carriage rates are high in parenteral drug users[7,8] and, on occasion, *P aeruginosa* has been grown from intravenous injection paraphernalia.[9] Among the many infectious complications related to parenteral drug abuse, pyogenic osteomyelitis and arthritis have emerged as difficult diagnostic problems with distinct bacteriologic patterns and types of joint involvement.[10-21]

Report of a Case

A 28-year-old man complained of a sharp, constant pain in his perineum and lower back for the preceding month, exacerbated by movement of his legs, lying on either side and weight bearing. Daily consumption of 18 aspirin tablets provided only minimal relief and he was often unable to sleep because of pain. He said he did not have fevers, chills or sweats, stating that apart from pain he felt well.

Three months before, he had fallen in the shower, sustaining a large bruise of his left thigh; however, he had been without discomfort for several weeks before the onset of his new symptoms and there were no other recognizable antecedent provocative events. He admitted to the intravenous use of amphetamines, morphine and pentazocine several times per week for several years, having used veins of his upper extremities exclusively for the preceding year.

He was afebrile with normal vital signs and in no distress except on weight bearing and with any active movements of the hips. Passive movement of either hip also produced pain, though of a somewhat lesser intensity. All joints were otherwise unremarkable and there was no lymphadenopathy. Apart from obvious intravenous "tracks," examination showed no other abnormalities.

Administration of ibuprofen, 400 mg four times a day, provided less pain relief than his prior aspirin use. On admission to hospital five days later, examination showed pain with movement of either hip or palpation of adductor muscles of the right thigh or over the symphysis pubis. There was pronounced weakness in adduction, flexion and extension of both hips, thought to be due to pain. His leukocyte count was 10,200 per μl, with 73% neutrophils, no band forms, 21% lymphocytes, 5% monocytes and 1% basophils with toxic granulations. Hemoglobin was 12.0 grams per dl, hematocrit 36% and platelets 493,000 per μl. A Wintrobe erythrocyte sedimentation rate (ESR) was 52 mm per hour. The serum aspartate aminotransferase level was 417 units per liter (normal, 5 to 35), with the lactic dehydrogenase value being 290 units per liter (normal, 100 to 230). The results of other serum and urine studies were normal, as was the chest roentgenogram.

Initial diagnostic considerations focused on a primary infectious process involving the hips, including septic arthritis, osteomyelitis or a psoas or appendiceal abscess. However, roentgenograms taken on admission and six days later of both hips, the pubic symphysis, sacroiliac joints and lumbosacral spine were interpreted as normal, specifically without evidence of joint destruction or osteomyelitis. A radionuclide bone scan showed only "slight" increased uptake in the symphysis pubis without other abnormalities. A gallium 67 scan likewise showed increased uptake in the pubic symphysis. A needle aspirate of the right pubic bone adjacent to the symphysis yielded a small amount of tissue that was inadequate for histopathologic examination. Cultures of the specimen, however, grew *P aeruginosa.* Cultures of three blood specimens showed no growth. After six weeks of a regimen of tobramycin given intravenously and ticarcillin disodium given via a Hickman catheter, the patient had no pain, fever, weakness or alteration in gait. Since discharge, he has been lost to follow-up.

Discussion

In parenteral drug abusers, *Pseudomonas aeruginosa* is a particularly common cause of pyogenic arthritis and osteomyelitis.[3,10-14,17,18,20,21] Kido and associates reported that 28 of 32 cases of hematogenous osteomyelitis in drug addicts in Los Angeles were caused by *P aeruginosa.*[13] Other case reports in the past several years have collectively supported a predilection for infection with organisms such as *P aeruginosa*[3,10-14,17,18,20,21] and *Serratia marcescens,*[15,16] organisms rarely seen in nonparenteral-drug-using adults with pyogenic arthritis or osteomyelitis.[1-5] The joint involvement in parenteral drug abusers is unique in that there is a propensity for fibrocartilaginous rather than synovial joints.[10-14,17-21] The reason for this is unknown. Those most commonly involved have been the vertebral,[13,18] sternoarticular[10,11,14,17,18] and sacroiliac joints.[10,12-14,18,19]

Osteitis pubis has been recognized in previously healthy children[22] and as a complication of pelvic and urologic surgical procedures, particularly suprapubic and retropubic prostatectomy.[23,24] In a recent review, 9 of 23 cases associated with urologic procedures were caused by *P aeruginosa* alone or in combination with other Gram-negative bacteria.[24]

Proposed pathogenic mechanisms for osteitis pubis have included antecedent trauma and impaired circulation. Steinbach and colleagues[25] used the technique of intraosseous phlebography to show venous drainage from the pubis in normal patients, those recovering from uncomplicated retropubic and suprapubic prostatectomies and in postoperative patients with osteitis pubis. This study showed that, in the latter group, there was considerable interference with venous flow from the pubic bone to the pelvic veins due to venous obstruction. Thrombophlebitis of the veins could be a cause of obstruction leading to venous stasis and resultant demineralization of the bone. In intravenous drug abusers, the mechanism for hematogenous localization in the pubic symphysis is unknown, although in some, injection of lower extremities or penile veins could lead to pelvic venous obstruction and provide a milieu for seeding from hematogenous infection.

This patient represents the 13th reported case of infectious osteitis pubis in parenteral drug abusers,[12,13,20,21] ten being reported in 1982 from two centers (Table 1).[20,21] All cases have been associated with *P aeruginosa* except for one that was caused by *S aureus,*[25] and another patient had generalized osteomyelitis due to infection with *Klebsiella.*[13]

The clinical features of the 13 cases of osteitis pubis in parenteral drug abusers have been consistent (Table 2). These cases present with an acute or subacute onset of moderate to severe pelvic, hip, thigh or groin pain exacerbated by weight bearing, active movements of the hip and pressure such as

TABLE 2.—*Clinical Features of Pyogenic Osteitis Pubis*

Prolonged, smoldering course is common
Local pain and tenderness without erythema or swelling are common (lack of local signs of infection)
Movement of hips causes pain
Obvious systemic signs of illness are often lacking
Prolonged intravenous drug abuse has typically preceded the illness
Previously recognized underlying disorders predisposing to infectious arthritis have not been present
Leukocyte count is usually normal, though the erythrocyte sedimentation rate is increased
Initial radiographs are frequently normal
Bacteremia is rare
Needle aspiration may be inadequate, thus necessitating bone biopsy
Pseudomonas aeruginosa is typically the responsible organism

from compression of the pelvis during examination or by lying on one's side. The emphasis of pain on hip motion may suggest a primary process involving the hip, diverting attention away from the actual site of involvement. Although pain may be less with gentle passive motion of the hip, sufficient pain may, nevertheless, be produced by minimal tension on the pubic symphysis created by this movement, reinforcing attention to the hip rather than the pubic symphysis.[2,12,20,21] This has also been recognized in cases of pyogenic sacroiliitis.[19] Additionally, pain referred to the suprapubic area may lead to investigation for a urinary tract pathologic process.[21] Temperatures and leukocyte count are typically normal or only minimally elevated. In all cases, however, the ESR has been increased. Therefore, localized musculoskeletal pain in a case of parenteral drug abuse and an increased ESR mandates an aggressive diagnostic investigation for osteomyelitis or infectious arthritis.

Initial radiographic studies of the pubic symphysis may be normal as exemplified by this case. Radionuclide bone scans, however, are usually positive at these times.[20,21] One exception has been reported.[20]

Blood cultures are often negative whereas cultures of aspirate or biopsy specimens from the pubic symphysis and adjacent bone usually show *P aeruginosa*. Biopsy is preferred because of its higher yield in fibrocartilaginous joints. Histologically, the process is a combined pyogenic arthritis and osteomyelitis of adjacent bone.

When *P aeruginosa* has been confirmed, treatment has included administering an aminoglycoside alone or in combination with carbenicillin or ticarcillin disodium.[20,21] It is unknown whether the addition of the latter antibiotics or open debridement[20] improves cure rates. Only four patients have been followed after hospital discharge and, in each case, after receiving antibiotics for four to six weeks without debridement, they had no evidence of recurrence.[21]

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Intraperitoneal Rupture of a Wilms' Tumor

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In 1943, in the *British Medical Journal*, Tanner[1] reported the case of a 6-year-old girl with abrupt and acute pain and tenderness of her abdomen from intraperitoneal rupture of a large Wilms' tumor. Because of her "hopeless condition," no resection was attempted and she died an hour after laparotomy. Our experience with a child of identical presentation shows the advances made in the past four decades in the management of this pediatric malignant tumor.

Report of a Case

A previously healthy 6-year-old girl was referred because of eight hours of severe abdominal pain and vomiting. There was no history of trauma. On examination she was acutely ill, clutching her abdomen and at times assuming a fetal position.

(Kosloske AM, McIver WJ, Duncan MH: Intraperitoneal rupture of a Wilms' tumor. West J Med 1985 May; 142:694-696)

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Submitted May 7, 1984.

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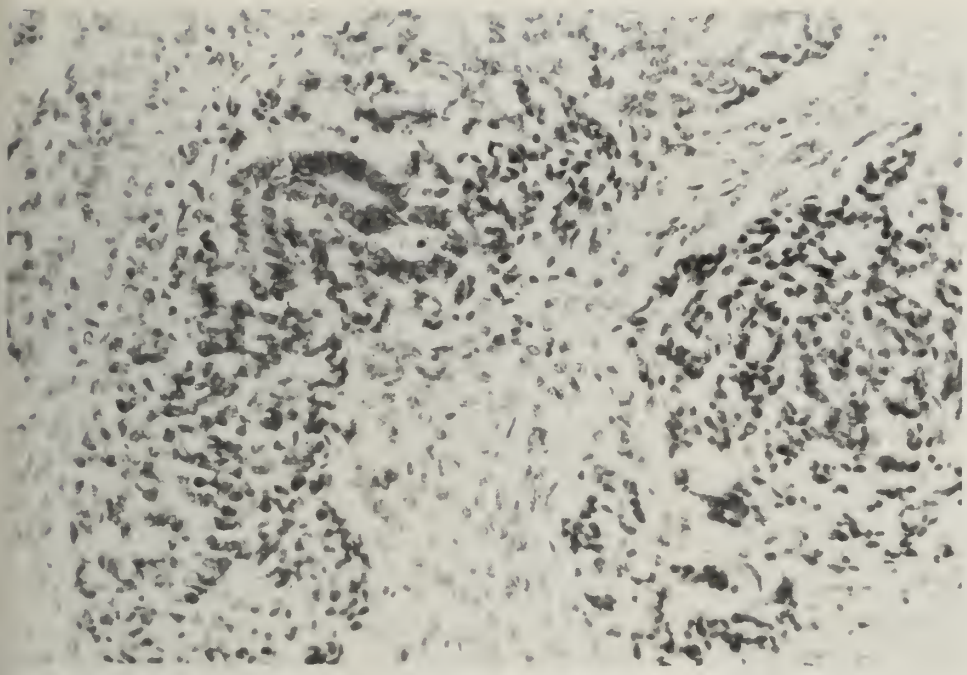

Figure 1.—Wilms' tumor, blastematous type, composed of immature mesenchymal and epithelial elements, with focal tubule formation (hematoxylin-eosin, × 250).

Her temperature was 37.8°C (100°F), pulse was 130 per minute, respirations 24 per minute and weight 19.5 kg (43 lb). The abdomen was slightly distended and very quiet. Guarding, tenderness and rigidity were present, particularly on the right. No mass was palpable. There was diffuse rectal tenderness. The leukocyte count was 16,000 per μl with a left shift.

Figure 2.—Abdominal x-ray film, upright view, showing intestinal obstruction. Metallic clips outline the margins of the massive tumor removed 11 days earlier. (Intussusception was suspected because of the report of Cox and Martin,[3] in which 4 of 16 cases of postoperative intussusception occurred after operation for removal of a Wilms' tumor.)

A diagnosis of probable perforated appendicitis was made and she was prepared for operation. The operative findings were hemoperitoneum, a normal appendix and an enormous tumor of the right kidney, with blood oozing from the site of spontaneous rupture on its anterior surface. Complete exploration was carried out via a long incision. Although the tumor was large and almost encircled the inferior vena cava, there were no metastatic nodules. A radical right nephrectomy was done, with biopsy of periaortic lymph nodes, exploration of the left kidney, an appendectomy and clipping of the tumor bed. She remained stable throughout the operation, during which she received 900 ml of erythrocytes and 1,400 ml of plasma and electrolyte solutions.

The tumor measured 10 by 13 cm, weighed 451 grams and had replaced the right kidney. It was primarily solid but contained some cystic, hemorrhagic and necrotic areas. Microscopic examination showed a Wilms' tumor of favorable histology, but with capsular and vascular invasion (Figure 1). Because of infiltration of the adrenal lymphatics, it was classified as stage IV.[2]*

Postoperatively she received chemotherapy with dactinomycin (actinomycin D), 15 μg per kg per day for five days, and vincristine sulfate, 1.5 mg per m^2 weekly, and radiotherapy. An intestinal obstruction developed on the 11th postoperative day (Figure 2). An ileoileal intussusception was suspected and reduced at operation. She recovered uneventfully thereafter. Radiotherapy (total, 1,050 rads) was completed and intensive chemotherapy was continued for 14 months. The tumor did not recur. Two years after cessation of chemotherapy, she is well, with no evidence of recurrent or metastatic tumor.

*J. B. Beckwith, MD, Children's Orthopedic Hospital, Seattle, and Chief Pathologist, National Wilms' Tumor Study, examined the tissue slides and classified the tumor.

Discussion

Nephroblastoma (Wilms' tumor) is the most common retroperitoneal malignant tumor of childhood. The usual presentation (80% to 90%) is an abdominal mass, although about 25% of children have abdominal pain.[4] The pain may be due to acute hemorrhage within the tumor, sometimes after trivial trauma. Rapid expansion of the tumor may be associated with fever, leukocytosis and anemia. Abdominal tenderness and guarding may obscure palpation of the underlying mass and may mimic acute appendicitis.

Spontaneous rupture of a Wilms' tumor is rare. In an analysis of 606 patients with Wilms' tumor,[5] 3% showed preoperative rupture, a designation that included both chronic disruption of the capsule by tumor growth and acute rupture with hemorrhage.

Operative management of this condition, encountered unexpectedly, requires excellent anesthesia and surgical expertise in pediatric malignant tumors. The surgeon may wisely decide to do a biopsy, secure hemostasis and close the abdomen in anticipation of removing the tumor later. If the decision is to proceed, a definitive operation must be done, consisting of radical nephrectomy, periaortic lymph node sampling and direct examination of the opposite kidney. The margins of the tumor bed are marked for the radiotherapist, using small clips that do not produce artifacts on computed tomographic scans. These steps are essential for proper staging of Wilms' tumor, which guides subsequent chemotherapy and radiation therapy.[2,4,5]

Exact staging of Wilms' tumor is important because the prognosis has improved dramatically in the past four decades. In 1938 Ladd[6] reported the cases of 11 long-term survivors among 45 children treated for Wilms' tumor. All the survivors had an operation and some had postoperative irradiation. The effectiveness of dactinomycin therapy following surgical intervention for this neoplasm was recognized by Farber and co-workers[7] in the 1950s. The current prognosis for a patient with Wilms' tumor when treated by a protocol combining surgical procedure, irradiation and chemotherapy is excellent. In the second National Wilms' Tumor Study, the two-year survival for patients with tumor confined to the kidney (group I) was 95%. Group II and III patients with local tumor extension had an 84% to 90% survival. Group IV patients with metastasis at the time of diagnosis had a 54% survival at two years when treated by combination therapy.[2] Even with intraperitoneal rupture, Wilms' tumor today is far from a hopeless condition.

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Correspondence

The Editorial Board will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words, and must be typewritten, double-spaced and submitted in duplicate (the original typescript and one copy). Authors will be given an opportunity to review any substantial editing or abridgement before publication.

The Profession's Future

To the Editor: I read Dr Ralph Crawshaw's Commentary "They All Laughed When I Spoke of Greedy Doctors"[1] in the February issue. The great tragedy of his colleagues' laughter is their lack of concern about the future of medicine. If many years of working together, honorable goals, hard work and commitment built up our profession, it is unfortunate that lust for money could be the major factor that will bring us down. The public is inundated with stories of staggering bills, unresponsive physicians, general arrogance and protectionism within organized medicine. As the government and insurance companies begin to take the control of health care out of the physician's domain, there is little complaining by the public. That is strong evidence that patient confidence is fragmentary—that we need to change our attitudes.

The laughter will die when fees are legislated—if we can't control it, others will—it's only a matter of time. But, perhaps that really is unimportant to those who milk the system—taking as much as possible and moving on is a common behavior among some men and women in business.

Dr Crawshaw shouldn't be disheartened—not everyone is laughing.

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REFERENCE

1. Crawshaw R: They all laughed when I spoke of greedy doctors (Commentary). West J Med 1985 Feb; 142:267

Cough Radiculopathy

To the Editor: It is hard to believe that the case of cough radiculopathy[1] reported in the September 1984 Correspondence section has thus far lacked comment.

The symptoms/signs suggest primarily a C-7 lesion, with a few overlapping signs/symptoms of C-6 and C-8 as is often the case with these lesions. The myelographic illustration was erroneous: rather than showing "an extruded disc and C-7 root compression," the findings were typical for focal spondylosis at C5-6. An extruded disk might have been present but I doubt that such could be inferred either from the myelogram that was shown or from the surgical approach that was used. One would wonder, given the references cited, why the surgical procedure was done posteriorly rather than anteriorly (and why "posterior" got into the text; is there an "anterior" laminectomy?). If the lesion was truly at C5-6 (as shown) rather than at C-7 (one presumes the authors mean the disk at C6-7) it would seem serendipitous that the cure cited would result from removal of the C-7 posterior arch alone.

Why do the authors use cases of lumbar trauma to qualify their thesis that the instant case resulted from cervical trauma (cough)?

Finally, just because pain developed when the patient was coughing does not necessarily mean that the coughing caused a disk herniation. It is common to see evidence of focal degenerative spondylosis without radiculopathy until some sufficient stimulus should bring out the symptoms/signs. In the cited case, one would suspect that the patient had a long-standing diskopathy which with "violent coughing" proved to be the straw that broke the camel's back and made the patient symptomatic.

Drs Torrington and Adornato are to be commended for suggesting another manifestation of cervical radiculopathy; their methods of presenting such leave much to be desired.

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REFERENCE

1. Torrington KG, Adornato BT: Cough radiculopathy—Another cause of pain in the neck (Correspondence). West J Med 1984 Sep; 141:379-380

* * *

Dr Torrington and Adornato Reply

To the Editor: We appreciate Dr Clark's astute perception of our unintentionally misleading illustration. The patient, in fact, had multilevel disk disease including C6-7. Although the major roentgenographic abnormality was at C5-6, her clinical symptoms and signs pointed to involvement at the C6-7 level. The success of the C-7 root decompression would validate our approach.

The precise mechanisms of trauma such as cough-producing radiculopathy are unknown. We used the example of cough-induced lumbar disk disease since the pathophysiology is most likely similar. There are no previous descriptions, to our knowledge, of cough producing cervical radiculopathy which was the original impetus for our report.

Finally, in reply to Dr Clark's point that the patient may have had some preexistent "diskopathy," we agree. There may have been some degree of degenerative disk disease present, as is often the case in 44-year-olds; on the other hand, it was asymptomatic until her tussive episode. The important aspect of the phenomenon is the recognition that cough can produce acute radiculopathy in the neck as it can in the lumbar spine.

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Cooperation Between Men and Women

TO THE EDITOR: I feel compelled to comment on the article by E. R. W. Fox concerning the superiority of women.[1] Why attack the aggressive nature of men and promote conflict when so much is to be gained by cooperation instead? Nearly all areas of human endeavor stand to benefit from a more even mix of men's analytical and women's verbal skills. Medicine in particular is making great progress by the increasing influx of women (my medical school class is composed of over 40% women). At a time when people are fed up with increasing technology and depersonalization of health care, the female contribution is saving the field through communication and compassion.

Surely, a similar essay on the superiority of men could also be written. I assume we agree that its publication would be inappropriate.

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REFERENCE

1. Fox ERW: On the superiority of women (Commentary). West J Med 1985 Feb; 142:266-267

Physical Examinations for Physicians

TO THE EDITOR: With regard to the article by Wells and co-workers on health screening of physicians,[1] the Palo Alto Medical Clinic requires its physicians to have annual physical examinations. Enforcement of this rule is simple and effective: if you don't do it, you don't get paid.

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REFERENCE

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Blood Loss After Thrombolytic Therapy

TO THE EDITOR: Clinical information comes from many sources including undesirable and unexpected side effects of drugs. Bleeding associated with anticoagulant therapy may herald unsuspected bladder or bowel carcinoma. We report a case in which bleeding with the thrombolytic agent streptokinase resulted in the diagnosis of large bowel carcinoma.

Report of a Case

A 63-year-old man presented to hospital with a complaint of swelling and pain in the lower right leg. A contrast venogram was carried out and showed a deep venous thrombosis in the right popliteal vein with extension of the clot to the pelvis. The patient had been in good health and review of systems was negative. He said there had been no signs of gastrointestinal bleeding.

Streptokinase therapy was instituted, consisting of 250,000 units given in an intravenous bolus, followed by 100,000 units per hour. Ten hours after the streptokinase therapy was started, large amounts of bright red blood began to pass through the patient's rectum. Streptokinase administration was discontinued. On subsequent evaluations, a well-differentiated adenocarcinoma arising in a villous adenoma of the sigmoid colon was found. An anterior sigmoid colon resection was done and a Duke's C lesion was found. Postoperatively he received minidose heparin therapy, then coumadin without complications. Eight months postoperatively he is doing well without evidence of metastases or recurrence of phlebitis.

Bleeding has often led to the diagnosis of a previously unsuspected anatomic lesion following anticoagulation with heparin or coumadin.[1,2] The use of thrombolytic agents generally carries a much greater risk of bleeding,[3] but it is unclear as to how often the bleeding is related to a preexisting important anatomic lesion such as colon cancer. We have cited one case in which a relatively new coagulation intervention led inadvertently to an important diagnosis. Further experience should help us decide whether gastrointestinal or genitourinary blood losses associated with such therapy require evaluation as is currently the case with heparin and coumadin administration.

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Therapeutic Pelvic Examination

TO THE EDITOR: Unusual pelvic pain relieved by pelvic examination has been reported previously.[1] The mechanism whereby the pain was relieved, however, is uncertain.[2] I report a case of pelvic pain unlike those previously reported which was successfully treated by pelvic examination.

Report of a Case

A 36-year-old woman (gravida 2, para 2) presented with severe menstrual cramps on the third day of her menstrual period. Her previous period had been unremarkable and the current period started exactly on the day she expected it. Her menstrual flow, however, was notably reduced compared with her usual periods. There was no fever, vaginal discharge or gastrointestinal or urinary tract symptoms.

On physical examination there was moderate suprapubic tenderness. Pelvic examination showed a small amount of blood in the vagina and what appeared to be a clot in the cervix. Findings on bimanual palpation of the adnexa were unremarkable. On bimanual examination of the uterus a small clot was dislodged from the uterine cervix followed by a deluge of uterine menstrual flow which splattered over the examiner's pants and shoes. At this time the patient spontaneously remarked on how miraculously her pain had vanished. Results of analysis of urine and urine pregnancy tests were negative. Pathologic examination showed only the blood clot.

Admittedly without incontrovertible evidence, I submit that this patient's pelvic pain was due to an obstructive blood clot at the uterine cervix which prevented her from having her normal uterine flow. The pelvic examination, on dislodging

the clot, provided normal drainage of the menstrual flow and immediate resolution of the pelvic pain.

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Another Preventable Endemic Condition

To the Editor: In a letter to the editor in the February issue,[1] Dr Martin C. Gregory states that death "from the unrestrained availability of handguns" is a preventable endemic condition that has an incidence "about 100 times higher in the United States than in comparable western countries." In response, I would like to call attention to another preventable endemic condition, one which is common among authors of articles in medical and other journals. This condition is characterized by the unsupported belief that the United States has the highest homicide rate in the world, one much higher than other western nations, and in addition a high suicide rate.

The FBI states[2] that the US homicide rate for 1982, the most recent available year, was 9.1 per 100,000 population. In comparison, the homicide rates were 9.6 in Sweden, 49.4 in Mexico and 126.2 in Zimbabwe.[3] In all, there were 17 nations with homicide rates higher than the United States. Our homicide rate peaked in 1980 and has declined each year since then, probably as a result of the aging of the population as well as stricter anticrime laws, but this improvement occurred in the absence of new gun-control laws. The United States never had the highest homicide rate, by a wide margin.

The situation in regard to suicide is equally interesting. The US suicide rate for 1982 was 12.0[4] and lay in the middle range, with about half of nations having higher rates. For example, the suicide rate for Hungary was 44.9, Denmark 31.6 and East Germany 30.5.[3] Adding homicide and suicide rates to get a "violent death rate" yields surprising results. Using this index, the US is less violent than 21 other nations, including Austria, Denmark, France, West Germany, Sweden and even Switzerland.

America is too violent, and we have much room for improvement. But this improvement will not come from action based on erroneous data and false accusations. It will come from carefully considered action based on facts. To hasten this improvement, we should do our best to reduce the incidence of inflation and distortion of mortality data, a condition that is preventable by exposure to measured doses of accurate data.

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Vascular Surgery and Diabetes

To the Editor: I enjoyed the recent article by Gleckman and Roth on diabetic foot infections.[1] As a practicing vascular surgeon, one of my most frequently seen problems is an infected foot, with associated advanced peripheral vascular disease, in a diabetic patient.

Infected ischemic ulcers of the foot often lead to progressive soft tissue infections, necrotizing fasciitis and osteomyelitis as described in the article. Diabetes intensifies the problem and antibiotics alone are rarely efficacious. Gangrene and amputation are the common conjoiners of this problem.

I would like to suggest to the authors that their team approach include a vascular surgeon. Amputations of infected limbs of diabetic patients with compromised circulation used to be commonplace. Today in most institutions they are rare. The significant variable is early intervention and revascularization before irreversible tissue damage.

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Topics in Primary Care Medicine

Pharmacotherapy of Asthma

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"Topics in Primary Care Medicine" presents articles on common diagnostic or therapeutic problems encountered in primary care practice. Physicians interested in contributing to the series are encouraged to contact the series' editors.

BERNARD LO, MD
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(Series' Editors)

Despite major recent therapeutic advances, asthma continues to be an important cause of morbidity and mortality worldwide. This persistent morbidity, despite the availability and widespread use of potent drugs that relax airway smooth muscle, has made it clear that airway smooth muscle contraction is only one component of the pathophysiology of asthma and does not by itself explain the clinical course of this disease. Both airway inflammation and mucus hypersecretion are prominent histologic features in patients dying of asthma, and both clinical and experimental evidence suggests that these factors play a major role in the clinical course of this disease. Although effective and reasonably well tolerated drugs are available to treat airway smooth muscle contraction, the current therapies for airway inflammation and mucus hypersecretion are much less satisfactory.

Bronchoconstriction

β-Adrenergic agonists are the most effective class of drugs presently available to inhibit contraction of airway smooth muscle. When administered by inhalation, even nonselective β-agonists such as isoproterenol cause potent relaxation of contracted airway smooth muscle in doses low enough to be free of significant systemic effects. Although a number of β_2-adrenergic agonists have been developed with relative selectivity for the β_2-adrenergic receptors present on airway smooth muscle, all of these drugs cause significant stimulation of β_1-receptors when they are given systemically in the doses required to relax airway smooth muscle. Furthermore, by causing relaxation of peripheral blood vessels (an effect of β_2-receptor stimulation) all of these agents can indirectly cause reflex tachycardia. Thus, the route of administration of a β-adrenergic agonist is a more important determinant of selective activation of pulmonary β-adrenergic receptors than is the pharmacologic specificity of the drug for β_2-receptors. Administration of these drugs by inhalation maximizes the desired effect—bronchodilation—and minimizes adverse effects. In contrast, oral, subcutaneous or intravenous administration of these drugs maximizes the potential for adverse effects for a given amount of bronchodilation. In theory severe bronchoconstriction could prevent adequate delivery of inhaled drugs to contracted airway smooth muscle, limiting the efficacy of inhaled β-agonists. In practice, however, administration of small doses of these drugs by inhalation has been repeatedly shown to be either more effective than or as effective as the systemic administration of considerably larger doses. Furthermore, in patients treated with adequate doses of an inhaled β-agonist, an additional systemically administered β-agonist causes little or no additional bronchodilation, even in patients with the most severe airway obstruction. Thus, there is little rationale for routine administration of β-adrenergic agonists by any method other than inhalation.

The optimal dose of each inhaled β-adrenergic agonist has not been determined and probably varies considerably among patients. For instance, in some patients with mild asthma, two inhalations of metaproterenol sulfate from a metered-dose inhaler have been shown to produce maximal bronchodilation, whereas in patients with more severe asthma a significant dose-response has been shown to occur with up to eight inhalations of the same drug. Prevention of *induced* bronchoconstriction, a primary goal of the outpatient management of asthma, may require considerably larger doses than those required to maximize baseline bronchodilation. Thus the dose and frequency of administration of these drugs must be tailored to each patient. Optimal therapy commonly requires higher doses and shorter dosing intervals than those recommended by the drug manufacturer. Thus some patients require as many as four or five inhalations of metaproterenol as often as every two to four hours. When patients know that certain activities (such as exercise or sexual intercourse) predictably trigger bronchoconstriction, it is reasonable to add a supplemental dose of an inhaled β-agonist 15 minutes before they begin. The patient should be encouraged to titrate the dose of

(Sheppard D: Pharmacotherapy of asthma [Topics in Primary Care Medicine]. West J Med 1985 May; 142:700-702)

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β-agonist upward (to a maximum of eight inhalations) until bronchoconstriction is reliably prevented or side effects occur. Although these high doses of inhaled β-adrenergic agonist frequently cause tremor or tachycardia, it is worth remembering that eight inhalations of metaproterenol, for example, deliver only one quarter of the dose contained in a single metaproterenol pill. Doses of inhaled β-agonists below five puffs rarely cause side effects.

Inhaled drugs can be administered by several different methods, including the metered-dose inhaler, the air-compressor nebulizer and intermittent positive pressure breathing (IPPB). The metered-dose inhaler is generally the preferred method because it is efficient, convenient, portable and minimizes dosing errors. When this device is used correctly, the resultant bronchodilation is at least equivalent to that achieved with the other methods. The major limitation to the use of the metered-dose inhaler is that patients frequently have difficulty mastering the correct technique. The patient should be instructed to hold the inhaler two inches in front of the mouth, to exhale first and then to activate the inhaler once while inhaling slowly. A ten-second breath-hold increases retention of the inhaled aerosol by increasing gravitational sedimentation. The inhaler should not be activated more than once during a breath. In fact, two puffs of a β-adrenergic agonist inhaled ten minutes apart have been shown to produce more bronchodilation than two puffs inhaled on successive breaths. Although with repeated coaching most patients can learn adequate (even if not perfect) technique, some cannot. In these patients, the use of available spacers can generally compensate for inadequate technique and allow effective use of a metered-dose inhaler. IPPB has no advantages over the air-compressor nebulizer and may rarely cause serious morbidity. It should thus not be used to administer bronchodilator drugs.

Theophylline and its metabolic precursors make up the other commonly used class of drugs thought to relax airway smooth muscle. In safe doses, these drugs are not as effective as β-adrenergic agonists either in reversing bronchoconstriction or in preventing induced bronchoconstriction. Like systemically administered β-adrenergic agonists, theophylline does not add significantly to the bronchodilation achieved by adequate doses of an inhaled β-agonist even in the emergency treatment of patients with severe airway obstruction. Theophylline does cause considerable toxic effects and occasional deaths when it accumulates in the blood stream in a high concentration. The principal toxic effects of theophylline are nausea, vomiting, tachycardia, anxiety and intractable seizures. It is thus difficult to justify the routine use of theophylline-containing drugs in the emergency treatment of acute bronchoconstriction. Recently, several studies have shown a potential beneficial effect of theophylline unrelated to bronchodilation—improvement in diaphragmatic contractility. If this effect is shown to be clinically important it may provide a rationale for the use of these drugs in selected patients with respiratory failure.

Although theophylline in commonly used doses is not as potent a bronchodilator as presently available β-adrenergic agonists, theophylline-containing drugs still have a role in the long-term management of asthma because of their long duration of action. Thus, whereas the longest acting β-adrenergic agonists presently available maintain maximal bronchodilation for only two to six hours, long-acting theophylline preparations can maintain maximal bronchodilation for 12 hours or longer. These drugs can therefore improve symptomatic control of asthma in patients who would otherwise require frequent high-dose administration of an inhaled β-adrenergic agonist. For similar reasons, long-acting theophylline preparations can be especially useful in patients with frequent nocturnal symptoms, or in patients with mild asthma who prefer the convenience of twice-a-day drug administration.

Whenever theophylline-containing drugs are prescribed the serum theophylline concentration should be periodically monitored to avoid inadvertent overdosing, since the pharmacokinetics of these drugs are notoriously variable both among patients and within any given patient. The simultaneous administration of numerous drugs, including cimetidine, allopurinol, erythromycin and propranolol hydrochloride, can significantly impair theophylline clearance and thus increase serum theophylline concentrations. Heart failure and hepatic dysfunction also impair theophylline clearance, sometimes greatly. Thus, if these drugs are administered to acutely ill patients who are in hospital and frequently receive other drugs, and who may have rapidly changing hepatic or cardiac function (or both), frequent monitoring of the serum theophylline concentration is mandatory.

When theophylline is administered to stable outpatients, it is reasonable to begin with a low dose (for example, 200 mg of a long-acting preparation such as Theo-Dur [anhydrous theophylline] every 12 hours for an otherwise healthy average-sized adult). The dose can then be adjusted upward if the patient's asthma is not adequately controlled and the theophylline blood concentration is less than 15 μg per ml. To avoid toxicity, an intravenous loading dose should not be given to patients who have been taking oral theophylline preparations and the initial maintenance dose for intravenous infusion should not exceed 0.5 mg per kg of body weight per hour. This dose should be cut in half in patients with liver disease or heart failure.

In patients with mild asthma, especially those with a predictable exogenous trigger for attacks such as allergens or exercise, therapy with cromolyn sulfate (one or two 20-mg capsules administered by inhalation four times a day or two capsules 15 minutes before exercise) can provide effective prophylaxis. However, inhaled β-adrenergic agonists are generally as effective as cromolyn in preventing exercise-induced bronchoconstriction and are considerably less expensive. In some patients the addition of cromolyn can reduce the dose of inhaled β-adrenergic agonist required to inhibit exercise-induced bronchoconstriction and can thus decrease the likelihood of side effects.

Although several other classes of drugs including calcium antagonists, α-adrenergic antagonists and muscarinic antagonists have been shown to reverse or inhibit bronchoconstriction, none of these drugs offers sufficient advantages over β-adrenergic agonists to justify their routine use in the treatment of asthma.

Airway Inflammation

The mechanisms underlying airway inflammation and edema in asthma are poorly understood. Consequently, there is little scientific basis for present approaches to treatment. Although the mechanism of the beneficial effect of corticosteroids on asthma is likewise poorly understood, these drugs are

thought to treat airway inflammation. This hypothesis fits well with the clinical observation that treatment with corticosteroids usually improves airway function in patients with status asthmaticus who do not improve after treatment with bronchodilators. The beneficial effects of corticosteroids do not occur until four to six hours after the start of therapy and may only become apparent after one or two weeks of continuous therapy.

The optimal initial dose of corticosteroid for the treatment of asthma has not been determined. Outpatients can often be effectively treated with the equivalent of 30 to 40 mg per day of prednisone. Some patients with severe prolonged exacerbations of asthma appear to require considerably higher initial doses. An initial dose of 60 mg of prednisone or an equivalent dose of methylprednisolone acetate every six hours is thus commonly recommended for patients who are sick enough to require admission to hospital for an exacerbation of asthma. Although corticosteroids are often administered intravenously to patients with status asthmaticus, prednisone is rapidly and completely absorbed from normal gastrointestinal tracts. In that the onset of corticosteroid action is slow (no appreciable effect on lung function occurs before four to six hours after administration), intravenous administration is often unnecessary. The optimal duration of corticosteroid therapy varies considerably among patients. Although some physicians prescribe a standardized rapidly tapering course of prednisone, this approach often results in early recurrence or inadequate initial improvement. It is preferable to continue the initially prescribed dose of corticosteroid until a clear-cut objective improvement in airway function has occurred. The rate at which to decrease subsequent steroid doses can then be individualized on the basis of the duration and severity of the patient's exacerbation and the patient's history of previous steroid requirements.

A recurrence of airway obstruction during or soon after a tapering course of corticosteroids usually indicates a requirement for long-term anti-inflammatory therapy. In many patients inhaled corticosteroids can eliminate or at least diminish long-term requirements for systemic corticosteroids. Because inhaled steroids are poorly tolerated during acute exacerbations of asthma, treatment with these drugs should be initiated when a patient's asthma is in remission (usually during a course of systemic corticosteroids). As with β-adrenergic agonists, inhaled corticosteroids have dose-dependent beneficial effects at doses well above those commonly recommended by their manufacturers. Thus, 24 inhalations per day (1,008 μg) of beclomethasone dipropionate are commonly effective in weaning patients from systemic corticosteroids who could not be weaned on a standard dose of eight inhalations per day. The increased incidence of oral candidiasis that results from the use of high doses of inhaled corticosteroids can be notably diminished if these drugs are inhaled through one of a number of commercially available spacers that diminish oropharyngeal deposition of the aerosol delivered from a metered-dose inhaler. The incidence of oral candidiasis may also be diminished if patients routinely wash their mouths with water after inhaling the drug. Because inhaled corticosteroids may cause bronchospasm, they are frequently administered after inhalation of a β-adrenergic agonist.

In patients who cannot be weaned from systemic corticosteroids despite the use of inhaled corticosteroids, inhaled cromolyn is occasionally effective. Alternate-day administration of corticosteroids has been shown to reduce the incidence of many of the complications of systemic steroid therapy. Because of the episodic nature of asthma, however, a stable alternate-day regimen is often difficult to achieve.

Despite the available methods for weaning patients from systemic corticosteroids, some patients with asthma continue to require long-term treatment with these drugs. The serious side effects that result underscore the inadequacy of the present approach to anti-inflammatory therapy in asthma and the urgency of developing more specific pharmacologic agents.

Mucus Hypersecretion

Although mucus hypersecretion is widely believed to contribute significantly to airway obstruction in status asthmaticus, none of our present therapies has been shown to treat this abnormality. Recent studies suggest that the most commonly used class of bronchodilators, β-adrenergic agonists, increases protein secretion from submucosal glands and thus increases the viscosity of mucus. This effect would not be expected to be beneficial. New information about the control of mucus and water secretion in the airways has suggested several possible pharmacologic approaches to mucus hypersecretion, but none has yet been studied in patients with asthma. Although hydration, airway humidification and chest physiotherapy have all been advocated to treat the consequences of mucus hypersecretion, these approaches have little scientific basis. None has been shown to produce clinical benefit in patients with asthma. The development of effective methods to treat mucus hypersecretion in asthma should thus be a major focus of future clinical research.

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Special Article

A Survey of Patient Satisfaction, Knowledge and Compliance

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A survey was carried out by telephone on 201 patients receiving continuing care from internists for commonly occurring chronic conditions. Although 90% of patients knew the names and therapeutic purposes of the drugs prescribed for them, only 30% could name any side effects to watch for. Almost 90% were satisfied with their physicians' explanations but only 58% actually had a good understanding of their condition. More than 90% complied with their drug regimen but only 39% adhered to the prescribed low-sodium diet and only 55% of diabetic patients tested their urines as instructed. Overall, degree of satisfaction and knowledge of their own condition did not correlate with degree of compliance.

Patients need more adequate education regarding their condition and potential side effects of drugs. More systematic attention should also be given to methods of motivating patients to comply with regimens that require a change in behavior.

(Sanazaro PJ: A survey of patient satisfaction, knowledge and compliance [Special Article]. West J Med 1985 May; 142:703-705)

It is axiomatic that effective care of patients requires both technical expertise—that is, diagnosis and treatment—and interpersonal or psychosocial skills.[1] The latter comprise the physician-patient relationship, patient education, counselling and the caring function. The psychosocial components are particularly important in the office management of patients with chronic diseases because the effectiveness of treatment for conditions like hypertension, diabetes mellitus and heart failure depends largely on patients' faithfulness in carrying out instructions correctly.[2-6] This in turn depends on the adequacy and accuracy of patients' knowledge of what they are supposed to do and on their motivation to carry out the advice. It is generally believed that patients' satisfaction with their physicians' services is one of the most important factors influencing patients' compliance.[6-10]

Although hospital and most office records contain information on the technical elements of care, comparable information on the interpersonal aspects of care is seldom recorded.[11,12] Even when such documentation is available, the actual impact of explanations and counselling can only be learned from the patients themselves. This report describes the use of a telephone survey to evaluate the satisfaction, knowledge and understanding of their condition and compliance of patients who were under the continuing care of internists for a variety of chronic conditions.

Methods

A series of questions was prepared to obtain information from patients on key factors reported to have a direct bearing on compliance.[1,4,6,8,10,13] The interviews were conducted by telephone rather than in person because of the former method's economy and demonstrated validity when used to obtain sensitive information from patients.[14,15]

On being informed of the purposes of the study and the safeguards of confidentiality, 26 internists in private, mainly fee-for-service, practice agreed to participate. Twenty were generalists and six were subspecialists with at least 50% of practice in general medicine. Samples averaging six patients per internist were randomly selected from office logs listing 125 consecutive, different patients seen in the office. All were receiving continuing care for a chronic condition, most commonly hypertension, diabetes mellitus, angina pectoris or chronic heart failure. Each physician was given the option of removing a patient's name from the list. Only a few names were deleted, primarily for reasons of deafness or other difficulty in communicating.

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A personalized letter signed by each physician informed each patient that a telephone survey was being conducted to learn how the physician might improve his/her services. The letter urged the patient to participate, assured anonymity and invited the patient to telephone the physician regarding any questions or reservations.

Three nurses and one well-qualified layperson were trained to conduct the interviews with reliability greater than .95. For each patient they had an accurate listing of the age, sex and principal diagnoses; the names, doses and schedule of drugs prescribed by each patient's physician, and the date of the last office visit.

Results

Of the 202 patients contacted by telephone, 201 agreed to be interviewed. Of these, 110 were women, average age 56.3 years, and 91 were men, average age 62.3 years. Each interview required an average of 12.9 minutes. A summary of the patients' responses to individual questions is shown by content area in Table 1.

More than 90% of the patients reported prompt access to their physicians by telephone, no difficulty in obtaining unscheduled nonemergency appointments and short waiting times in the office. In all, 95% of patients correctly named the drugs they were taking or identified them by reading the labels on the containers. Almost 90% correctly stated the medical purposes of each drug—that is, getting rid of fluid, lowering blood pressure or blood sugar or reducing the work of the heart. In contrast with this high percentage, only 29.6% correctly described one or more of the common side effects of these same drugs.

Almost 90% of patients were entirely satisfied with the explanations they had received regarding their own condition and with their physicians' willingness to answer questions. About 80% felt that their doctor took enough time with them, although 8% of patients commented that their physician was or seemed rushed. About 80% of patients stated that their physicians treated them as persons, not merely as cases. Patients who said their physicians answered their questions satisfactorily and spent enough time with them had no greater understanding of their condition than did those who felt these elements were lacking. Only 57.7% of the patients had a good understanding of their condition—that is, knowing that controlling high blood pressure by restricting salt and taking the drugs as prescribed will help prevent strokes, heart failure or kidney failure. Patients with diabetes mellitus were considered to have a good understanding of their condition if they stated the equivalent of "by following the diet, taking my insulin (or oral agent) as prescribed and testing my urine sugar, I will help prevent complications that might later cause loss of vision, heart or kidney disease or loss of circulation in the legs."

A total of 64 patients (31.8%) stated they did not expect their doctor to treat them as persons. The relation between expectation of being treated as a person and being so treated was statistically significant ($\chi^2=80.9$, $P< .001$). More than 90% of patients reported taking the drugs as prescribed, but only about two fifths of those on a low-salt diet claimed to follow this strictly. Slightly more than half of the patients with diabetes mellitus stated they carried out tests of urine as frequently as instructed. Approximately the same number were able to describe at least three important rules regarding foot care. On statistical analysis, the degree of patients' satisfaction and understanding of their condition was not related to their compliance with either a low-salt diet or urine testing.

TABLE 1.—*Summary of Responses in 201 Patients Interviewed*

Content of Questions	No. of Patients	No. of Correct or Positive Responses	Percent
Availability of Physician			
Ready access by telephone	201	188	93.5
Nonemergency appointment same day	128	99	77.3
Nonemergency appointment in 48 hours	128	23	18.0
Waiting time in office <15 minutes	201	132	65.7
Waiting time 15 to 30 minutes	201	53	26.4
Patient's Knowledge of Prescribed Drugs			
Knows names	199	189	95.0
Knows purposes	199	179	89.9
Knows side effects	199	59	29.6
Patient's Knowledge of Own Condition			
Understands own condition	201	116	57.7
Knows rules of foot care (diabetic patients)	67	38	56.7
Patient Satisfied			
With physician's explanation of condition	201	180	89.6
With physician's answering of questions	201	178	88.6
With physician's taking enough time	201	157	78.1
With being treated as a person	201	160	79.6
Compliance			
With drug regimen	199	181	91.0
With low-salt diet	166	65	39.2
With urine testing for sugar	58	32	55.2

Discussion

The sample of patients in this study cannot be considered representative of all patients receiving care from internists, although their three most common diagnoses—hypertension, diabetes mellitus and ischemic heart disease—account for a large proportion of care provided by internists nationally.[16] Further, the 26 internists were all located in one geographic area and all but a few were in fee-for-service private practice.

In sharp contrast to the results of the telephone survey commissioned by the American Medical Association, the great majority of patients in this sample expressed a high degree of satisfaction with all aspects of their care.[17] This included ease of access, ready availability of their internists, adequate explanations, satisfactory answers to questions, "plenty of time" spent by their physicians in their care and being treated as a person. These are the factors that are commonly reported to be associated with higher degrees of compliance.[1,4,6,8-10,13] In this sample, however, the low compliance rates for low-salt diets by patients with hypertension and various forms of heart diseases and for urine testing by diabetic patients were no different from those generally reported.[7,13,18]

Injuries to patients from drugs account for 11% of total indemnity in claims of professional liability.[19] The finding that less than a third of patients in this sample had any knowledge of side effects of prescribed drugs suggests that physicians have not yet fully appreciated the importance of this aspect of patient education.

This study showed the relative cost-effectiveness of the telephone interview as a direct means of obtaining information on patient compliance and the several factors believed to influence patient behavior in following or disregarding a regimen. Assurance of anonymity and a helpful nondirective form of questioning by appropriately trained interviewers with a good telephone manner induced all but one of the 202 patients in this sample to discuss frankly what many of them had not been able to bring to their physician's attention. Despite the widely prevalent caveats regarding inaccuracies of patients' self-reported compliance behavior, the evidence is persuasive that a nonthreatening manner and a display of genuine interest can induce patients to report honestly on their nonadherence to instructions.

The results of this study are consistent with the growing body of literature defining the special efforts that must be made by physicians to achieve good patient compliance.[3,6,7,10] A good relationship with patients and providing sound education and advice are clearly necessary but are not in themselves effective in inducing patients to comply with advice that requires a change in behavior beyond simply taking medicine. Other important factors also affect patients' decisions to follow, modify or ignore instructions. These include feedback to patients, open communication and nonjudgmental attitudes when questioning patients about compliance, reminders and cueing, reinforcement, graduated implementation of a complicated therapeutic program and other behaviorally oriented strategies.[10,20-22]

The information obtained from each internist's sample was reported to that internist in summary form, along with the aggregate results of the entire survey. This enabled each participant to learn how well he or she was doing in the psychosocial domain of patient care as compared with other internists. This kind of comparative, individualized feedback has been shown to help physicians improve their care of patients.[23]

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Commentary

Autopsies by Primary Practitioners

A Solution to the Decline in Autopsies?

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The postmortem examination—its art and science—has a long and revered history. It is probably the major instrument that brought medicine out of its Dark Ages. Before the age of specialization, the postmortem examination was carried out to great advantage by a wide variety of physicians. Since the age of specialization, it has become the province of pathologists. Indeed, in the past decade it has become the primary province of medical examiners, as autopsy rates have dropped precipitously in most hospitals.[1] The reasons for the decline in autopsies have been thoroughly discussed, evaluated, explained and deplored.[2-6] There seems to be general agreement that autopsies are still important tools. Numerous studies have documented that over the past three decades there has been a fairly constant rate of diagnoses found at autopsy that were not known previously. This rate generally runs about 10% in spite of newer predeath diagnostic techniques.[7-9] In spite of the exhortations of many, the decline continues and no practical solutions have been proposed.

In remote areas without a resident pathologist, the autopsy rate is virtually zero except for coroner's cases that necessitate transportation to a regional center. Human nature seems to dictate that something good is not appreciated until it is taken away. Our medical staff, sorely missing the advantages of autopsy, decided to do our own gross autopsies locally and send the tissue specimens off to our reference laboratory. As a tool of teaching and discovery, this has been well received by our medical and nursing staff.

A cited cause of the decline in autopsies is the lack of clinician interest in the procedure and findings. I propose that having interested primary practitioners do the dissection and gross pathological interpretation could be a solution to the waning interest in autopsies.

Methods

We selected cases for autopsy on the basis of minimal potential legal involvement. We believe that it is inappropriate for a nonpathologist to give legal testimony on postmortem data. That is, any patient who may be a coroner's case or any case in which there would possibly be a malpractice suit was rejected. This basically means that the patients must have been in the hospital for more than 24 hours as inpatients and that death must have occurred more or less expectedly. Autopsies are carried out at the local funeral home, which has a well-equipped preparation room. Appropriate permits are obtained. Policies and procedure were set up by the medical staff. The autopsies are done whenever feasible, usually within 12 hours of death, sometimes after-hours in the evenings, sometimes early in the mornings. Because autopsy technique is usually a part of basic medical school pathology, refreshing on the procedure is not difficult. I had cooperation from the King County Medical Examiner's office and our consultant hospital pathologist in renewing my autopsy technique. In all, since the introduction of autopsy to our hospital, we have done three postmortem examinations that were very beneficial to our staff, physicians and other professionals. We notify as many hospital professionals as possible. We invite emergency medical technicians, nurses, physicians and laboratory personnel to observe. Gross pathologic study is carried out and interpreted by me. Specimens for microscopic pathologic examination are sent to our reference laboratory where our consultant pathologist studies them. After completion, a clinical-pathological conference is held and a postmortem summary is completed by the pathologist.

Reports of Cases

Case 1

A 51-year-old man had been known to have severe emphysema for 17 years. He died after a prolonged period of terminal respiratory failure. Protease inhibitor studies on the family and patient were negative. The autopsy diagnoses were severe pulmonary emphysema, passive congestion of the liver, generalized arteriosclerosis with old focal myocardial infarction and mild nephrosclerosis. Nothing totally unexpected was shown by the autopsy. However, it was of great benefit for the nursing staff, many of whom had never seen an autopsy nor the classical findings of chronic lung disease.

Case 2

A 72-year-old man had had very little in the way of regular health care. He was known to be a heavy smoker and drinker. He was admitted to hospital with transient focal neurological findings and general debility. On x-ray studies a mass was noted in the upper portion of the left lung. Results of

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needle biopsy of the upper lung mass were difficult to interpret but thought to show squamous cell carcinoma. Shortly after the biopsy, the patient became comatose and after five days died in the hospital. The autopsy results showed pulmonary blastoma with tumor embolism to the gastric artery and secondary ulceration, as well as tumor embolism to the anterior cerebral circulation. He had mild emphysema, coronary atherosclerosis and passive congestion of the liver and spleen. In this case, the autopsy brought forth a diagnosis that would not have been known without the postmortem examination. Indeed, pulmonary blastomas are extremely rare tumors.

Case 3

A 78-year-old man was admitted to hospital with a problem of general debility, malnutrition and anal fistula. The patient had neutropenia and, at various times, was felt possibly to have Felty's syndrome or a possible bone marrow abnormality. The patient had a gradual downhill course ending in coma and death. On autopsy there were classical findings of hepatic cirrhosis, portal hypertension with varices and ascites, gallbladder stones, severe coronary atherosclerosis and lobular pneumonia of the right lower lobe. At the clinical-pathological correlation, gathering together the knowledge of several physicians involved, it became quite evident that the patient had a severe problem with alcohol. All of the other problems were probably due to the long history of alcohol intake. In this case, the clinical-pathological correlation greatly clarified the major problem of this patient.

Discussion

Determining the cause of death is the traditional purpose of autopsy. The use of the postmortem examination has many benefits beyond this. Garcia and Wilmes[3] have shown that pathologists can apply techniques such as electron microscopy and immunocytology in deciphering difficult cases and to expand medical knowledge. In our experience (primary care) the autopsy has great benefit in reviewing anatomy and pathology and in clarifying the primary problems of our patients. In the three examples, a rare tumor was discovered and attention was refocused on the patients' primary problems. These cases must certainly have a beneficial effect on patient care.

We found that autopsies carried out by an interested primary care practitioner were quite stimulating and beneficial to the hospital community in general. We also feel that an autopsy done by an interested nonpathologist is still better than no autopsy at all. In remote areas autopsies must be done by nonpathologists. However, in more populated areas autopsies carried out by practitioners in cooperation with a pathologist may be a solution to the declining interest in autopsies. Clearly, not all practitioners will have the time or interest to participate and some find such studies repulsive. Autopsies carried out by interested nonpathologist practitioners would spread the burden of these nonrevenue-producing procedures around to several departments and stimulate clinicians by more direct involvement. In addition, perhaps educational credit could be extended to autopsy participants. There are some positive steps that can be taken to reverse the decline in autopsies.

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Commentary

The Return of Two-Class Medicine—Ill Effects of Medi-Cal Reform

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California's drastic Medi-Cal reforms have created great difficulties in health care for the poor. Patients' clinical problems seldom are apparent in descriptions of changes in public insurance programs. Rapidly escalating costs of Medi-Cal led to irresistible pressures for reform, especially from the business community. The new Medi-Cal regulations provide for prospective contracts with hospitals for inpatient services, the transfer of "Medically Indigent Adults" to the responsibility of county governments and various other straightforward funding cutbacks. Confusion, disruption of services and adverse health outcomes have accompanied the Medi-Cal reforms.

(Waitzkin H: The return of two-class medicine—Ill effects of Medi-Cal reform [Commentary]. West J Med 1985 May; 142:708-709)

The brief case histories that follow illustrate some typical difficulties since the "reform" of Medi-Cal (California's Medicaid system). Such clinical problems seldom come to light in general descriptions of changes in public insurance programs.[1-3] These histories all involve patients at a community clinic that is a teaching site of the University of California, Irvine. The clinic serves a largely low-income and minority population in southern California.

Case Histories

• Mr S is a 31-year-old man with severe insulin-dependent diabetes mellitus. During the past several years, his vision has deteriorated to the point that he now is nearly blind. He has cooperated in a job retraining program for the blind and has learned the technique of blood sugar monitoring at home, to obtain better control of his diabetes. On January 1, 1983, his *monthly* deductible charge under Medi-Cal increased from $50 to $250. This change means that he no longer can afford his regular medical visits or the supplies needed to check his blood sugar at home. Even the purchase of insulin and syringes has become difficult under the new deductible.

• Mr C is a 55-year-old man who had worked regularly during his entire adult life as a communications worker. He lost his job in April 1982 as part of a general layoff at his company. As he looked for a new job, he began to experience a high level of anxiety. One month after he lost his job, his health insurance ended. About five months later, severe chest pain suddenly developed and the patient was admitted to a local hospital with an acute myocardial infarction. Medi-Cal covered this hospital stay. On January 1, 1983, his classification under Medi-Cal changed to "Medically Indigent Adult." He no longer was eligible to receive care from his own physician or the hospital that had treated him for the heart attack. Diagnostic studies that his cardiologist thought were necessary to assess his potential for rehabilitation were disapproved by Medi-Cal. Because of the change in Medi-Cal status, pharmacies would not fill his prescriptions for heart medications until an appeal was granted after a month's delay. Meanwhile, two ambulance visits to emergency rooms were required because of bouts of chest pain.

• Mrs C, a 55-year-old part-time clerical worker who is married to Mr C, has moderate hypertension treated for many years with medication. In January 1983 she began to have episodes of severe throbbing pain in the back of her head. As a Medically Indigent Adult under Medi-Cal, she no longer could go to her previous doctor and was eligible only for emergency room visits in situations that would "threaten life or cause serious disability." On two occasions she went to an emergency room, but Medi-Cal regulations would not permit the diagnostic tests and follow-up visits that the doctors in the emergency room thought were necessary to rule out brain disorders or complications of hypertension.

• Mr H is a 44-year-old man disabled from injuries in a motor vehicle accident 12 years ago. During September 1982 his appendix ruptured and peritonitis developed that required extensive surgery and antibiotic treatment. In February 1983 he began to have recurrent abdominal pain, fever and oozing

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from his surgical scar. When he called his surgeon's office, the receptionist told him that the surgeon no longer was accepting Medi-Cal patients because the hospital at which the surgeon operated had not received a Medi-Cal contract for inpatient services. Over a three-day period, Mr H traveled to five doctors' offices and clinics before finding a place that would accept him as a patient and treat his wound infection.

• Mr P is a 64-year-old man who is an "undocumented" worker from Mexico. During the past four months he has noted increasing difficulty in urinating. On physical examination, he was found to have an enlarged prostate gland that may contain a tumor. His blood tests show that his kidney function is deteriorating because of urinary obstruction by the prostate. He needs prostatectomy, a relatively simple operation that probably could correct his kidney abnormalities. However, no local hospital will admit him for the surgical procedure unless he applies for Medi-Cal. In the past, when eligibility screening for Medi-Cal has revealed that a patient is "undocumented," the Immigration and Naturalization Service (INS) periodically has obtained this information and has instituted deportation proceedings. Administrative changes during 1983 and 1984 have streamlined the process by which Medi-Cal notifies the INS, and deportation proceedings have increased in frequency. For these reasons the patient feels that he cannot jeopardize his family by entering the hospital. If he returned to Mexico, he would have no health insurance for hospital treatment. Presently there is no resolution to this problem, and the patient's kidney function continues to worsen.

Discussion

These patients all suffer in one way or another from the chronic and recurrent financial crisis of government resulting in part from the rising costs of the Medi-Cal program. By 1982 Medi-Cal accounted for approximately one eighth of the annual state budget in California. Meanwhile, tax revenues for the state were increasing very slowly, because of both Proposition 13 (which lowered property taxes) and the severe economic recession. The California legislature in 1982 anticipated a budget deficit of $2 billion, yet lawmakers were reluctant to raise taxes. The Medi-Cal program provided a target for budget cutting.

During the 1982 legislative session, pressures for reform became irresistible. The leadership of the California Assembly choreographed the enactment of a complex series of new laws and regulations that provided for drastic changes in the Medi-Cal system. These laws passed despite vigorous opposition from the California Medical Association and the California Hospital Association.

Confusion and disruption of services have been hallmarks of the Medi-Cal reforms so far. Problems like those of the patients in the case histories are typical. People who have been going to a particular doctor and hospital for many years find that they must go elsewhere, or that they cannot receive Medi-Cal at all. In some counties, patients with chronic medical conditions like hypertension and diabetes learn that they can receive health care only when they go to emergency rooms or need admission to a hospital. For others, the increase in the monthly deductible under Medi-Cal makes it impossible to see a doctor. Many people, especially those in the Medically Indigent Adult category, find it difficult to figure out where and under what circumstances they can obtain care. A prospective study has shown serious, adverse health outcomes among diabetic and hypertensive Medically Indigent Adult patients since the enactment of the Medi-Cal reforms.[4]

"Two-class medicine" has returned. An inadequately financed and chaotic public system serves the poor, while a friendly and solicitous private sector reaches the well-to-do with private insurance.[5]

It is time to return to an ethical question. Is health care a right of all citizens—analogous, for example, to public education? This question has been debated for several decades but never resolved. At present, national policy clearly has moved away from accepting the principle of health care as a right. But the problem remains. As dissatisfaction and suffering become more widespread, organized resistance and political change become more likely. At that point, health care as a right should get back on the agenda of national policy. If and when it does, reconstruction of the nation's health-care system would be an appropriate goal.

The United States is the only major economically developed nation that has not adopted some type of national health system with universal coverage.[6] Such a system in this country is an ambitious goal. But ultimately it is the only direction that will not perpetuate the same kinds of difficulties that we face now. Confronted by the suffering in our midst, can we aim toward anything less?

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Public Health and Preventive Medicine

Thirty-seven Miles Up Highway 70

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One of a series of articles from western state public health departments

Emergency medicine and prehospital medical services continue to share a leadership position in the rapid technologic advancement that is occurring in the provision of total health care.

In the past 15 years an eruption of new concepts, enhanced equipment and technical advances have come to this specialized corner of science we call emergency medicine. Categories of emergency medical technicians and paramedics were developed to "extend" the physician into the field. Specialized ambulances, communications equipment and life-support systems were developed, modified and improved to meet the need of emergency medical providers. At the same time new emphasis was placed on the hospital phase of emergency care. Advanced cardiac life support and advanced trauma life support training was provided for physicians, nurses and support personnel. We learned of the efficacy of trauma centers, which should be designated and where these centers should be located.

Now that the concept we call an emergency medical services system has been developed and widely implemented, it is time to fine-tune the system and look for gaps that were initially overlooked. One may begin by looking over the skyscrapers and through the smog of the cities out into the open spaces and mountains that are common features for us in the western United States.

We find an obvious discrepancy in the way the system works between urban-suburban areas and our remote wilderness emergencies. It is assumed, and expected, that a call to "5th and Broadway" in a large city will be handled promptly and efficiently by a coordinated emergency medical service system involving many agencies. We may find fire department "first-responders" quickly arriving on the scene, followed in minutes by ambulance service paramedics with hundreds of pounds of costly advanced-life-support equipment and medications. Shortly following arrival, the vital exchange of information occurs between on-scene personnel and the base station physician at the nearby resource hospital, and we may even find a hospital-based helicopter (or two) hovering overhead. Within minutes the victim becomes a patient and is being whisked through town to the most appropriate hospital that has been previously categorized to handle this particular type of critical care problem. But what about the call that comes in as "37 miles up highway 70, then left on county road 416, four miles up the dirt road and onto the rocky ledge on the left"?

Almost all western states have mountainous areas growing up from otherwise flat terrain in which towns are generally located, whether it be Sacramento, California; Carson City, Nevada; Olympia, Washington; Salt Lake City, Utah, or Ten Sleep, Wyoming.[1] But can these western states boast that a fully integrated emergency system has been worked out to care for the inevitable severe injuries and illnesses that occur in remote mountainous areas? Experience indicates there is a wide variation of emergency services available among individual geographic areas of a given state, ranging from a totally integrated rescue-medical system to a hodgepodge of responders.

In some areas the local ambulance service is called to mountain injury or illness calls only to find itself undertrained and underequipped to handle an extended technical rescue, while a formal organized mountain rescue squad may sit by idly, not getting a call to help.[2] This lack of interagency coordination is sometimes more prevalent than local officials would like to admit, but can be solved by periodic meetings, such as through a local emergency medical services council with representation from all conceivable resources.

Mountain rescue and medical treatment is often measured in hours or even days rather than the minutes it takes in cities and towns. Commonplace items on ambulances in town, such as "scoop" stretchers, large drug boxes and 11-kg (25-lb) electrocardiographic telemetry transmission communications units cannot be used in remote mountain emergencies because of weight and size restrictions to the animal or human being having to carry them. Other factors to be considered include food, water and shelter for both the patient and the attending medical personnel. Time factors also dictate that a patient's

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condition may have to be addressed more thoroughly and treated far more aggressively. This necessitates providing additional training and physician authorization to the medical personnel for administering and monitoring medications and treatment. Catheterization may not be the norm at 5th and Broadway, but it is a realistic consideration when the patient is in the mountains, seven hours from the closest hospital.

The mountains also pose certain medical problems with which emergency medical personnel must be familiar through their physician advisor. One is acute mountain sickness (high-altitude disease), manifesting itself as either pulmonary or cerebral edema, or both.[4-7] Acute mountain sickness has been described at altitudes as low as 2,500 m (8,000 ft) and can range from illness and discomfort to death.[4-7] Following recognition of the syndrome, a controlled descent from the elevation, oxygen and some medications are utilized in appropriate treatment.[5]

Another common mountaineering problem is hypothermia, generally related to extended exposure to cool weather and the associated wind-chill factor, or to immersion in the cold water of mountain rivers and lakes. The impaired mental state and physical function associated with hypothermia could lead to death if not properly recognized and treated. Personnel must be able to recognize signs and symptoms of hypothermia and treat a patient with heated oxygen, administer IV solutions and limit a patient's movement so as to not increase the "after-drop" effects.

High-altitude mountain medical care also taxes equipment. Plastic items such as air splints become hard and brittle, oxygen in tanks becomes uncomfortably cold and IV solutions also become cold and refuse to run properly.

The prime concern then is recognizing that mountain medicine is different from day-to-day city emergency medical services—in the technical problems associated with it, the psychologic conditions to a patient and the need of extensive preplanning.

It is incumbent on governmental public health care officials and private-practice physicians involved in emergency medical services to be amply concerned that a uniform coordinated effort is in place to efficiently respond to patients in the wilderness setting. In too many locations, the search-and-rescue component has been isolated from the day-to-day emergency medical services transport component. Every agency and organization should know the existence and technical skills of all the others. Cross-training between rescue and medical personnel should be standard. Radio communication interfaces should be planned to allow for interagency dialogue. A list of resources should highlight all vital facts: where are horses, snowmobiles or helicopters available? How do you most easily get access to the impressive capabilities of military installations that have fixed-wing aircraft, helicopters or flight surgeons? Where are physicians, nurses or paramedics who might respond with the rescuers to provide advanced life-support to a patient?

Within a relatively small number of years, we have made tremendous strides in improving life expectancy and reducing needless death in cities and in the smaller towns throughout the United States. It is now time to insure that coordinated lifesaving efforts go beyond the city limits into the plains and mountains, *before* the emergency occurs.

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Medical Schools of the West

The UCLA School of Medicine

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One of a continuing series of reports from the medical schools of the West

The aims and values of the University of California, Los Angeles (UCLA), School of Medicine were formulated as follows in its *Institutional Self-Study* published in 1980:

- To provide high-quality education for undergraduate and graduate students preparing to serve in all branches of medicine;
- To contribute to the production of outstanding teachers of these disciplines;
- To foster biomedical research.

Thus the school's raison d'être is to sustain a faculty, a diversity of students and an environment conducive to the discovery and sharing of knowledge relevant to medicine.

The faculty and facilities of the school also accommodate the following related goals:

- To educate students in fields cognate to medicine, such as biochemistry, physiology and pharmacology;
- To contribute to the education of students of dentistry, nursing, public health and other health fields;
- To provide the highest quality of medical care and preventive medicine, from primary medical care to tertiary diagnosis and treatment, in response to the needs of individuals and of society;
- To address such problems as the organization and availability of medical services; the distribution of medical care as to specialty and geography; the lifelong education of physicians and other health professionals;
- To strengthen the intellectual life of UCLA and the University of California;
- To contribute to the world's progress towards health and peace through the international exchanges of students and faculty and the education of foreign students and fellows who return to their countries.

The subcommittee on objectives for the Institutional Self-Study Task Force concluded its write-up with the following summation:

> The school is concerned with problems of human beings and society. It tries to respond to the needs of the community, the region, the nation, and, to some extent, the society of nations. At the same time, the Task Force firmly holds the belief that pursuit of knowledge for its own sake, without immediately apparent social relevance, is rightly the province of many of the school's faculty members. Respect for such research is frequently essential for recruitment of the most inspiring teachers. Moreover, history teaches us that the ultimate benefit to mankind of such research is unforeseeable, indispensable and incalculable.

Research

From its conception in the late 1940s the new medical school on the UCLA campus was destined to make an early and enduring mark in research. It came into being when the nation was entering its post-World War II era of unprecedented public interest in and support for biomedical research (Figure 1).

Exemplary of interdisciplinary research at UCLA are tissue typing and positron emission tomography (PET). UCLA investigators developed a systematic method of human leukocyte antigens typing and were the first to apply it to renal transplantation. They originated the microcytotoxicity assay, now the worldwide technique for serologic typing, and identified new histocompatibility antigen specificities. Automated instrumentation designed for the typing of sera has wide applications in the burgeoning field of monoclonal (pure) antibody production.

The dramatic new nuclear medicine technique of positron emission computed tomography originating at UCLA is a benign, relatively noninvasive process that combines external radiation detection with mathematical image reconstruction to show the relationship among function, metabolism and structure. PET records the three-dimensional distribution of injected radionuclide emitted from a patient and portrays on a television screen a vivid cross-sectional picture of biochemical activity that can be coordinated with computed tomographic studies to show function and structure relationships. It may also be correlated with neurologic, cognitive and behavioral findings. The short-lived isotopes that PET requires are made by UCLA's biomedical cyclotron—one of the few in the nation close enough to a hospital to be practical for human

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ABBREVIATIONS USED IN TEXT

CME = continuing medical education
NIH = National Institutes of Health
PET = positron emission tomography
UCLA = University of California, Los Angeles
VA = Veterans Administration

use. So far, PET has been mainly used in studies of the heart and the brain.

In the Department of Anatomy abnormal orientations of anterior hippocampal pyramidal cells have been found in the brains of schizophrenic patients. Structural sex differences in the brain are showing how the hormonal environment in embryonic rats determines different brain development in male and female rats. Vision research is clarifying the senescence of the pigment epithelium and degenerative diseases of the macula and retina. The reticular formation in the brain was found to be of vital importance in sleep, arousal and focusing attention.

Developments from the Department of Anesthesiology include a noninvasive method of estimating pulmonary blood flow in anesthetized patients; techniques for monitoring catecholamines that improve anesthesia efficacy and safety; a new neuromuscular blocking agent, and a noninvasive transcutaneous oxygen monitor.

Researchers in the Department of Biological Chemistry were the first to determine the importance of histones in the structure of chromosomes. Determinations of the structure of pituitary thyroid-stimulating and pituitary luteinizing hormones have led to better diagnostic immunoassay methods, including one that detects elevated levels of prostatic acid phosphatase in patients with prostatic carcinoma. Studies of glycoproteins and glycolipids of cell surfaces have revealed the mechanism through which specific viruses recognize and infect target cells. Some mechanisms of DNA damage and repair have been detailed.

UCLA was among the first medical schools to recognize the essentiality of computers to progress in health sciences and to create (in 1967) a strong Department of Biomathematics. Developments here include innovative statistical methods for tissue transplantation research; plotting radiation treatment and screening for carcinogens in cancer research, and new biomathematical processes for exploring how diseases are inherited and how drugs and other metabolites circulate in the body.

Investigators in the Department of Medicine have discovered genetic defects of erythrocyte metabolism responsible for nine kinds of hemolytic anemia. Defects of cholesterol metabolism in leukocytes have been correlated with some kinds of atherosclerosis. Fetal pancreatic transplants in rats signify progress towards future islet transplants in humans to treat patients with diabetes mellitus. An innovative balloon flotation catheter that is threaded into the heart has revolutionized the care of patients with acute cardiac disease. Acquired immune deficiency syndrome was first characterized at UCLA. A unique human T-cell line (named Mo) that produces most of the known lymphokines and activates host-defense cells has been developed. The role of peptide hormones in the gastrointestinal tract, brain and retina has been clarified. The International Olympics Committee awarded a contract to Clinical Pharmacology for testing drug use by athletes in the 1984 Olympic games in Los Angeles, and the resulting capability is proving useful in many areas of research.

In the Department of Microbiology and Immunology, workers have shown that the herpes simplex virus travels in nerve axons, establishes latent infections in the sensory ganglia and can be reactivated from this site. Findings from inserting cloned treponemal genes and cloned influenza hemagglutinin genes in *Escherichia coli* are leading to more exact immunizations. Studies in tumor immunology have shown that cell-mediated cytotoxicity of tumor cells is mediated by soluble factors released by cytotoxic cells. Genes and gene products of some viruses involved in virulence for various organ systems are being defined. Individual genes from virulent agents are reinserted into the DNA of avirulent viruses and the function of the corresponding gene product is studied. The cloning and expression of influenza virus genes in bacteria and animal cells are increasing the knowledge of how these viruses reproduce and may lead to a genetically engineered flu vaccine.

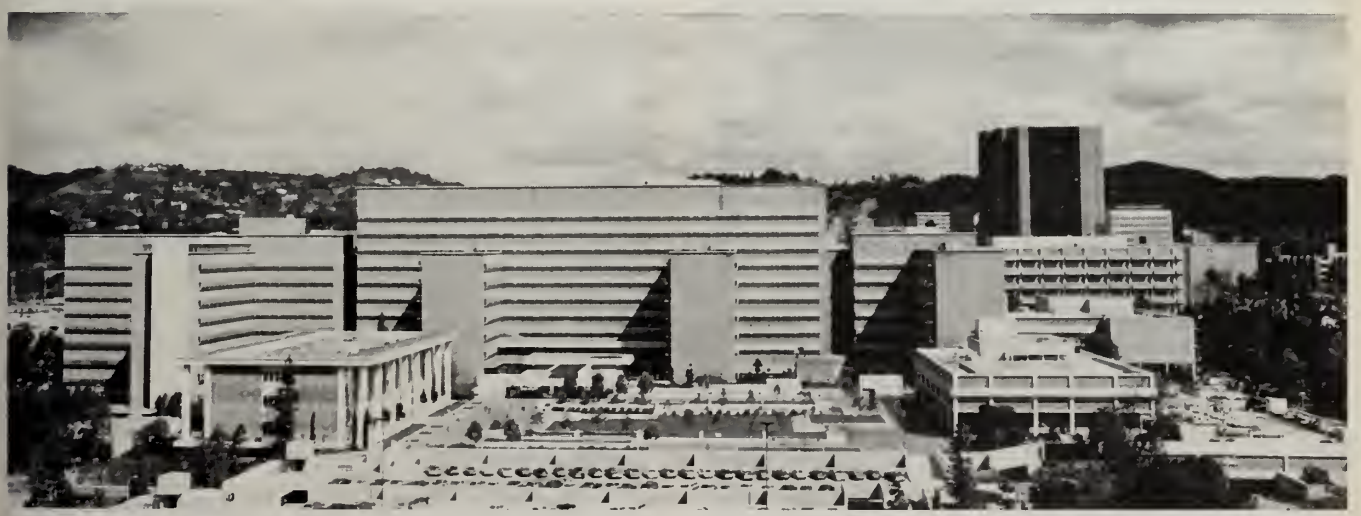

Figure 1.—The UCLA health sciences complex facing north to the UCLA campus and the hills of Bel Air. The building on the front left shows the portasanta marble exterior and classical colonnades of the Jules Stein Eye Institute. The building on the front right is the Marion Davies Children's Clinic. The medical center looks over the Neuropsychiatric Institute and Reed Neurological Center on the left and the School of Dentistry on the right. Towering over the complex on the far right is the Jonsson Comprehensive Cancer Center.

The Department of Neurology, long a center for interdisciplinary work in epilepsy, has been designated a comprehensive urban epilepsy center by the National Institutes of Health (NIH). PET scans are improving the pinpointing of seizure foci and surgical treatment of patients with partial complex epilepsy is proving safe and effective in selected cases. Other research is focused on the basic causes of demyelinating diseases such as multiple sclerosis and myoneural junction diseases such as myasthenia gravis.

Clinical investigators in the Department of Obstetrics and Gynecology are adding to knowledge of the endocrine precursors of endometrial cancer, endocrinologic changes in menopause, basic physiology of mother and fetus in pregnancy, the management of cases of ovarian cancer, cancer chemotherapy, biochemistry of the amniotic fluid, biochemical delay of premature labor and anatomical principles in correcting pelvic support. Studies of ovulation induction use the ultrasound monitoring of follicular development, and a program of in vitro fertilization initiated in 1983 has achieved a pregnancy rate of 30%.

The Department of Ophthalmology (Jules Stein Eye Institute) is 1 of 12 participants in the nationwide Retinitis Pigmentosa Study. Investigations are under way on the mechanism of vitamin A transport, immune mechanisms of the retina, differentiation of retinal photoreceptors, retinal cyclic nucleotide metabolism, and gene mapping. Other research by UCLA ophthalmologists includes the management of glaucoma, corneal infections and transplants, heredofamilial aspects of retinal disease, biochemistry and biophysics of the crystalline lens, ophthalmic ultrasonography, diabetic retinopathy (in conjunction with the nationwide Early Treatment Diabetic Study), ocular herpes simplex and autoimmune disorders. Research is improving helium ion heavy-particle irradiation for choroidal melanoma.

Researchers in the Department of Pathology have found that aging is regulated by the same master control system of genes that influences immunity and are seeking ways to modify the aging process. Other research explores cancer, viral disorders, arteriosclerosis, bone disease, immunopathology, renal disease and the chemistry of erythrocytes.

Investigators in the Department of Pediatrics have reported the first successful use of a drug to close the patent ductus arteriosus of some premature infants. A reversible cellular immunodeficiency has been identified in malnourished infants and children. Home parenteral nutrition has provided a model for worldwide adaptation. Advances have been made in hemodialysis and ambulatory peritoneal dialysis and in renal transplantation. The two-dimensional echocardiographic imaging technique for noninvasive diagnostic testing for congenital heart disease developed here is now widely used at cardiac centers. Basic and clinical research has yielded valuable findings in fetal and perinatal thyroid physiology, screening for congenital hypothyroidism, thermogenesis in the newborn, surfactant biology, replacement therapy for hyaline membrane disease and the role of pituitary peptide, catecholamine and carbohydrate metabolism in the neonate. Other problems explored are the pathogenesis and taxonomy of chondrodystrophic dwarfism, hereditary transmission of diabetes mellitus, genetic screening and prenatal diagnosis of Tay-Sachs disease and the molecular biology of gene activation and repression. Research also goes ahead on the ontogeny of leukocyte movement, the epidemiology of group B streptococcal infection of mother and newborn and the pathogenesis of persistent viral infections of the central nervous system and multiple sclerosis.

In the Department of Pharmacology discoveries have been made on the role of pituitary, thyroid and adrenal cortical hormones in opiates and addictions to other drugs. β-Endorphin, a 31-amino-acid peptide with morphinelike properties, has been found to increase plasma level of prolactin but not growth hormone, to lower blood pressure and heart rate, to improve depression modestly and not to affect schizophrenia. The ability of steroids to reverse drug-induced down-regulation has been documented and the possibility of receptor up-regulation in cases of rebound hypertension after clonidine withdrawal is under investigation. A new compound called xylamine has been developed and is being used to identify a protein in neuronal cell membranes that transports transmitter from the cell's outside to its inside. This could be the first radioactive tool for studying the presynaptic nerve terminal—the site of action of psychoactive drugs. The gas chromatography-mass spectrometry facility, conducted jointly with the UCLA Brain Research Institute, collects data on compounds as a function of their concentrations. Such data have important uses in controlling environmental carcinogens, accuracy of biomedical research and optimal safety-efficacy of medication.

In the Department of Physiology new methods for measuring heat production in contracting muscles and assessing underlying chemical changes have been designed. Work on the ionic compartments in cardiac muscle, especially calcium ions, which determine the intensity of excitation-contraction coupling in the myocardium, has elucidated the action of digitalis. The development of the electron microprobe analysis has allowed quantitation of different ions in a cell and the picoliter or "microdroplet" analysis of many elements important in nephrology and gastroenterology. Studies in epithelial transport physiology are illuminating lithium transport in the understanding of manic-depressive diseases. Knowledge of the molecular mechanisms of ionic specificity in membranes has been applied to excitatory phenomena. Other research is extending physiology as a central biomedical science—spanning the range from molecular mechanisms to whole-body regulation of human life in health and disease.

In the Department of Psychiatry and Biobehavioral Sciences research on mental function and dysfunction extends from molecular biology to cultural anthropology—with special emphasis on alcoholism, mental retardation, schizophrenia and childhood psychoses. An "intelligent speech prosthesis" has been developed for persons with aphasia. Improvements in the psychiatric diagnosis of the elderly have helped discover treatable conditions. New ways to predict drug effects in selected patients with severe psychiatric illnesses have been charted and a diagnostic instrument that detects incipient dyskinesia from psychotropic medication has been found.

In the Department of Radiation Oncology a new fast-neutron therapy facility, one of four in the nation designed for clinical research, is being constructed. Intralymphatic immunotherapy (using cultured allogeneic melanoma cells) has produced evidence of clinical response in metastatic melanoma. Limb salvage and bone marrow transplantation are increas-

ingly successful, and a γ-teletherapy knife has proved valuable in treating small intracranial lesions. Radiation biology is being studied in a large germ-free animal laboratory.

In the Department of Radiological Sciences a new diagnostic image-processing laboratory combines computed tomography, nuclear magnetic resonance, positron emission tomography, digital radiography, ultrasound, x-ray and other conventional imaging techniques in carrying out diagnostic image analysis.

In the Department of Surgery an endorectal ileal pull-through operation with internal ileal reservoir for treating some forms of ulcerative colitis and multiple polyposis has obviated bladder dysfunction and impotence from proctocolectomy and avoided a permanent ileostomy stoma. Splenic conservation and repair, including partial splenectomy, have been refined to the point they are now standard in this country and many others. The right-angle Hopkins rod telescope that allows better visualization of the larynx, nasopharynx and upper respiratory tract has been adopted widely. On-line computer analysis of nystagmus helps in the understanding of vestibular dysfunction. Bone morphogenetic protein is showing promise for bone regeneration and cell differentiation. Total knee, hip and shoulder replacements are steadily proving more effective and clinical trials of a new fixation system for resurfacing hip joint replacements are yielding good results. Advances in surgical oncology include the clonogenic assay for testing the sensitivity of tumor cells to chemotherapeutic agents; the preservation of limbs by preoperative administration of doxorubicin (adriamycin) hydrochloride, followed by irradiation and en bloc resection, and hyperthermia for treating extensive cancers in visceral organs.

Education

The initial target class size of 128 first-year students (increased some 10% by transfers to the third-year class) was reached in 1968. By then, however, a looming physician shortage primed an increase to 144 first-year students in 1972. National expansion of medical education in the 1970s proved overextended in the 1980s, and the UCLA class size has now been reduced to 140 (Figure 2).

Each year since 1979 as many as 24 medical students in the University of California, Riverside-UCLA Biomedical Sciences have joined the UCLA medical curriculum after their third year of undergraduate education at Riverside. In 1981 the first annual group of as many as 24 students in the Charles R. Drew Postgraduate Medical School-UCLA School of Medicine program entered the first year of the UCLA medical curriculum, taking the first two years at UCLA and the last two years at the Drew-King Center. The 24 Drew students are included in the 140 first-year places at UCLA and the 24 Riverside students are in addition to the 140.

With the graduation of 173 seniors in the class of 1984, 2,999 physicians have earned the MD degree at UCLA. Since 1970 the percentage of women and minorities has greatly increased. Some 90% of the alumni stay in California to practice. Other states they prefer are Hawaii, Alaska, Colorado, Arizona, Texas, Washington and Oregon above all, and on the East Coast, New York, Massachusetts and Maryland. About 10% of UCLA graduates are in faculty positions in the United States. Alumni include department chairpersons, health administrators, NIH research chiefs and practicing physicians in all disciplines. The medical school is proud of all its graduates and grateful for their services to medicine and society (Figure 3).

The first medical curriculum at UCLA conformed to the pattern of American medical curricula (two years of basic sciences, then two years of clinical clerkships) that had changed little since 1920. By the 1960s it was seen at UCLA that this rigid structure could no longer contain the informa-

Figure 2.—Sherman M. Mellinkoff, MD, Dean of the UCLA School of Medicine since 1962.

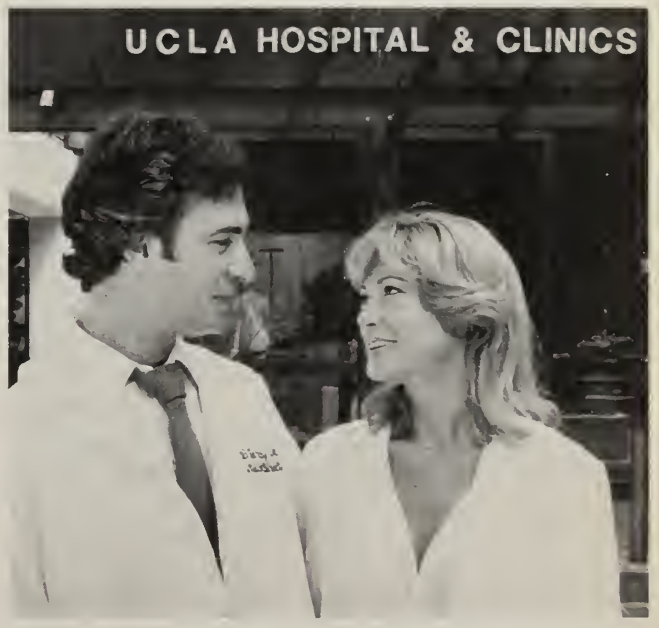

Figure 3.—UCLA medical alumni David Barcay (class of 1976), director of emergency medicine at Midway Medical Center in Los Angeles, and wife Barbara Hayden (class of 1980), plastic surgery resident at UCLA.

tion explosion resulting from accelerating discoveries in biomedical research and the desire of medical students for greater freedom of choice. A curricular revision committee (chaired by David H. Solomon, MD) designed a new curriculum that started the third year of clinical clerkships in the summer following the sophomore year and reserved three quarters for electives. The new curriculum was started in 1966 for the first-year class of 1970. In 1975 another innovation combined the last two years in a "clinical continuum" consisting of four quarters of required clerkships and three quarters of electives.

The junior-senior clinical continuum aims at giving students maximum freedom to realize individual interests consonant with mastering the basic clinical training essential for physicians in general. This is achieved by blending 50 weeks of required clinical clerkships with 28 weeks of electives; 16 weeks are available for vacation. Required clinical clerkships are in medicine (12 weeks), surgery (12 weeks), pediatrics (6 weeks), obstetrics and gynecology (6 weeks), psychiatry (6), primary-care preceptorship (2), neurology (2), radiology (2), dermatology (1) and ophthalmology (1). The following three types of electives are offered: advanced clinical clerkships; advanced clinical clerkships with primary patient responsibility (subinternships), and depth electives. Depth electives, many interdepartmentally organized and taught by both clinicians and basic scientists, emphasize clinical skills along with the pathophysiology and molecular factors in disease processes and may be research oriented. Most electives are of four weeks' duration and many entail prerequisite clerkships.

The elective curriculum helps selected students to earn the PhD degree in the course of their medical education. Completion of the MD-PhD program takes six to seven years, depending on the thesis research.

Students participate in shaping the curriculum by membership on the Educational Policy and Curriculum Committee and other committees affecting the curriculum. (Students have served on key committees of the school since 1968.) The appointment of Norman Cousins to teach the patient-physician relationship from the standpoint of the patient has enhanced the humanistic resonance of the curriculum.

Integral to the curriculum are the lively preceptorship and ubiquitous one-to-one seminars on clinical logic that UCLA's superb house officers give the medical students. Physicians on the volunteer clinical faculty selflessly share their hands-on expertise and clinical wisdom with both medical students and house officers.

A farflung network of affiliated hospitals richly extends the 711-bed UCLA hospital and 209-bed UCLA Neuropsychiatric Institute as a great classroom for the clinical continuum. The affiliates were indispensable to the medical school in its early years when it relied on Harbor General Hospital (now Harbor-UCLA Medical Center) in Torrance (California) and on the neighboring Wadsworth Veterans Administration (VA) Medical Center for general clinical training, on Saint John's Hospital in Santa Monica for obstetrics and gynecology and the Santa Monica Hospital for emergency medicine. Today the affiliates are just as essential, as they afford the wide diversity of educational opportunities inherent in the clinical continuum. The school's partners in turn benefit from the influence of a teaching program on patient care, and by the eventual return of some former medical students to practice at or near a favorite affiliate.

Harbor-UCLA (owned and operated by the County of Los Angeles) and the Wadsworth VA Medical Center continue to be among UCLA's closest affiliates. Other Los Angeles County affiliates are the Charles R. Drew-Martin Luther King Jr Medical Center and the Olive View Medical Center. Other VA affiliates are the Brentwood and the Sepulveda VA medical centers. Community hospitals affiliated with UCLA include Cedars-Sinai Medical Center, Santa Monica Hospital, Orthopaedic Hospital, Shriners Hospital for Crippled Children, Children's Hospital, Daniel Freeman Memorial Hospital, the Kaiser Foundation hospitals of Los Angeles, West Los Angeles and Panorama City, St Mary Medical Center in Long Beach, Northridge Hospital Medical Center, St Francis Medical Center, Valley Presbyterian Hospital, Venice Family Clinic, Jewish Home for the Aged of Los Angeles, Freda Mohr Multiservice Center, City of Hope Hospital in Duarte, Kern Medical Center in Bakersfield and Ventura County General Hospital in Ventura.

Both the research and education missions of the medical school are advanced by important special programs at UCLA, some of which also provide direct community service. These include the Mark Taper Center for Health Enhancement, the UCLA-University of Southern California Long Term Care Gerontology Center, the Crump Institute for Medical Engineering, the Pulmonary Rehabilitation Center and the Center for Ulcer Research and Education (CURE), founded by the late Morton I. Grossman.

The Department of Continuing Education in Health Sciences conducts continuing medical education (CME) programs responsive to the needs of practicing physicians in the community. The department emphasizes problem-solving case management rather than the comprehensive format previously favored. A new trend is workplace-related CME presented in the hospital or a physician's office.

* * *

Columnist Jack Smith wrote that UCLA is "one of the great learning centers of the world; a city within a city, not only emanating its intellectual energy to the metropolis that surrounds it, but also attracting and absorbing the life and vitality of that metropolis. In a sense, UCLA is the heart and source of Los Angeles." The medical school's union with that "heart and source of Los Angeles" gives it the creative energy to realize the vision of its founders, faculty, graduates and friends.

The Absence of Hematuria in Patients With Symptomatic Urinary Tract Stones

PATRICK M. DUNN, MD
ROBERT T. KELLER, MD
STEPHEN R. JONES, MD
Portland

OUR PERSONAL experience with a patient who had symptomatic urolithiasis but a normal urinalysis prompted a search of the literature to determine how frequently urinary tract stones occur without hematuria. We found that gross hematuria is reported to occur in 33% of patients with urolithiasis.[1] The occurrence of microhematuria in such cases is believed to be 90% to 95%, but this information is based on anecdotal experience.[2] The uncertainty of these data is reflected by the vague statement in most textbooks that hematuria is "almost invariably present" or "the rule" in patients with urinary tract stones. To better define the incidence of hematuria in patients with symptomatic urolithiasis, we did a retrospective review of inpatient and outpatient populations.

Patients and Methods

Inpatient Evaluation

Hospital records were used to identify all patients at Good Samaritan Hospital and Medical Center of Portland, Oregon, from August 1978 to March 1983 with a discharge diagnosis of renal or ureteral calculus. In all, 80 patients were identified and their records were reviewed. Patients were included in the study only if all of the following criteria were met: the hospital admission was required because of abdominal, back or groin pain; this was the patient's first known episode of urolithiasis; urolithiasis was documented by intravenous pyelography or by collection of a stone (or both), and a "clean catch" (noninstrumented) urine specimen was submitted to the Good Samaritan Hospital laboratory on admission. Patients were excluded from the study if any one of the following criteria were met: the initial urine specimen was not obtained in a clean-catch manner; the patient was a woman who had menses or dysfunctional uterine bleeding at presentation; the patient had "vigorously" exercised within one day of urine collection ("vigorous" was defined as any activity significantly greater than that of daily living[3]), or there was any recorded history of renal or genitourinary disease including benign prostatic hypertrophy, urinary tract infection within three months of the initial evaluation, abdominal or back trauma within three months of presentation, glomerulonephritis, malignant hypertension, polycystic disease, tumor, papillary necrosis, vascular abnormalities, sickle cell anemia or bleeding disorders. Of the 80 patients, 24 (30%) fulfilled all inclusion and exclusion criteria. All of the urine specimens had been delivered to the laboratory at Good Samaritan Hospital. Each urine specimen was evaluated chemically with Chemstrip 6 (Bio-Dynamics) and "no blood present" was considered normal. Then 12 ml of urine was centrifuged at 2,000 rpm for five minutes and microscopic examination was done by certified medical technologists on the 0.5-ml sediment; 15 to 20 high-power fields (×400) were reviewed on each specimen. Normal values were defined by the laboratory as zero to two erythrocytes and zero to five leukocytes per high-power field.

Outpatient Evaluation

We reviewed all outpatient records between January 1967 and January 1983 with a diagnosis of renal or ureteral calculus contained in the 5% randomly selected medical record sample of the Portland, Oregon, Kaiser Permanente Health Care Center. We identified the records of 175 such outpatients and evaluated 171 (98%). Of these, 52 patients (30%) met all inclusion and exclusion criteria. These criteria were identical to those described for inpatient evaluation except that outpatient urine specimens were examined by the Kaiser Permanente laboratory. Chemical testing was done with Multistix (Ames Division of Miles Laboratories, Inc) from 1967 to 1980 and with Chemstrip 9 (Bio-Dynamics) from 1980 to 1983. The absence of blood was considered normal. The microscopic urine examination was done on the sediment of 8 to 12 ml after five minutes of centrifugation at 3,500 rpm and normal values were identical to those of the Good Samaritan Hospital laboratory.

In both phases of investigation, the following data were recorded for each patient: age, sex, date of presentation, analysis of the initial clean-catch urine specimen for gross and chemical blood and number of erythrocytes and leukocytes per high-power field. The following data were recorded if available: previous urinalysis results, urine culture, location of calculus (renal pelvis, ureter or bladder), size of calculus and composition of calculus (analyzed by the Louis Herring Company of Orlando, Florida).

Results

The frequency of hematuria in patients with symptomatic renal or ureteral calculi is shown in Table 1. Of the inpatient population, 7 of 24 (29%) had zero to two erythrocytes per high-power field, as did 7 of 52 (13%) of the outpatient population. Six of 24 (25%) of the hospital-evaluated group and 19 of 52 (37%) of the non-hospital-evaluated patients had no chemical hematuria. Of the seven inpatients with normal microscopic urine examination, six were negative and one was trace positive for blood. Similarly, six of the seven outpatients with zero to two erythrocytes seen had no chemical

(Dunn PM, Keller RT, Jones SR: The absence of hematuria in patients with symptomatic urinary tract stones [Information]. West J Med 1985 May; 142:717-719)

From the Department of Medicine, Good Samaritan Hospital and Medical Center, Portland.

Reprint requests to Patrick M. Dunn, MD, Department of Medicine, Good Samaritan Hospital and Medical Center, 1015 NW 22nd Ave, Portland, OR 97210.

TABLE 1.—*The Urinalysis in Patients With Urolithiasis*

	Hematuria									Pyuria	
	Microscopic (RBC/HPF)					Gross		Chemical		(WBC/HPF)	
	0-2	3-5	6-10	10-30	>30	+	−	+	−	0-5	>5
Inpatient (24)											
Number	7	1	0	6	10	3	21	18	6	18	6
Percent*	29	4	0	25	42	13	88	75	25	75	25
Outpatient (52)											
Number	7	3	7	7	28	5	47	33	19	45	7
Percent*	13	6	13	13	54	10	90	63	37	87	13

RBC/HPF = erythrocytes per high-power field, WBC/HPF = leukocytes per high-power field, + = positive, − = negative

*Due to rounding out of the percentages, not all groups will add up to 100% (range, 99%-101%).

hematuria. Gross hematuria was not present in 21 of 24 (88%) of the inpatients and 47 of 52 (90%) of the outpatients evaluated. Significant pyuria was present in 6 of 24 (25%) of the inpatients and in only 7 of 52 (13%) of the non-hospital-evaluated group.

The major reasons for study exclusion were a previous history of renal calculi or no documentation of urolithiasis. Urinary tract infection was rarely associated with stones in these patients. The mean age, sex, mode of diagnosis, stone location, size and composition of both the inpatient and outpatient populations are shown in Table 2.

Discussion

Symptomatic urolithiasis is a common clinical problem not frequently confused with other abdominal conditions because of the unique quality and distribution of the pain. Many times, however, classic symptoms are not present, and the clinician must rely on laboratory information. The urinalysis is a simple, time-honored test used in the diagnosis of urolithiasis. The presence of blood in the urine of a patient with abdominal pain has strongly suggested this diagnosis and, conversely, the presence of a symptomatic stone has meant that hematuria was "invariably" present.

Our investigation has better defined the sensitivity of the urine examination in patients with symptomatic renal or ureteral stones. Only 71% of inpatients and 86% of outpatients had hematuria on initial presentation. These values are less than previously reported. Gross hematuria was present in 13% of hospital-evaluated patients and in 10% of non-hospital-evaluated patients, percentages that are much less than previously stated.[1] Clinicians should appreciate that hematuria is not invariably present in a patient with symptomatic urolithiasis. A missed or delayed diagnosis will be avoided by continued consideration of renal or ureteral stones even if the urine specimen contains no blood.

We found appreciable differences in the incidence of hematuria in the inpatient and outpatient populations. The inpatient group was more likely to have difficult diagnostic and therapeutic problems. The absence of hematuria added to the diagnostic confusion and probably increased the likelihood of hospital admission.

The outpatient population provided information about a less select and more relevant patient group. Less than 25% of these patients were eventually admitted to hospital for acute pain and many of these were admitted because the absence of hematuria obscured the actual diagnosis.

No correlation can be made between stone size or composition and the absence of hematuria as the number of patients without hematuria is too small for evaluation. There was no relationship found between calculus location and gross hematuria, contrary to the belief that stones in the renal pelvis are more likely to cause visible blood in the urine.[4] Significant pyuria with urolithiasis is infrequent in both the inpatient (25%) and outpatient (13%) populations, despite this being a "common" finding in anecdotal reports.[4]

The reason for the absence of hematuria in patients with urinary stones is not known. It has been reported that some of these patients do not have hematuria because the calculus has created complete obstruction.[5] In our study, however, there appeared to be no correlation between complete ureteral obstruction and the absence of hematuria. We repeatedly noted that hematuria was closely correlated with a patient's maximal pain. Increased pain possibly correlates with increased uromucosal excoriation or distention by the stone, which causes increased bleeding. Similarly, patients with diminished pain have a reduction or absence of blood in the urine, probably due to decreased urothelial damage. For example, a 26-year-old woman was admitted to hospital for abdominal pain and had no hematuria. Two hours later, she had severe pain and a second urine specimen showed 3+ blood and 320 erythrocytes per high-power field. A third specimen submitted hours later during another episode of severe pain was unchanged and she subsequently passed a small calculus with resolution of her pain and hematuria. This correlation be-

TABLE 2.—*Age, Sex, Mode of Diagnosis and Calculus Specifications*

	Inpatient N=24	Outpatient N=52
Mean age (yr)	42	43
Sex (♂:♀)	1:1	2.7:1
Diagnosed by (%)		
Intravenous pyelography	96	90
Calculus collection	54	46
Both	50	36
Calculus		
Location (%)		
Renal pelvis	8	11
Ureter	75	85
Both	17	4
Size (mean diameter, mm)	1 to 9	1 to 7
Composition (% calcium oxalate)	100	95

tween pain and hematuria was noted in five other patients. To increase the likelihood of "catching" the hematuria, it may be reasonable to obtain the urine specimen during the period of maximal pain, collect serial urine specimens or do a timed urine collection. Prospective evaluation of this problem is needed.

The incidence of hematuria in patients with a symptomatic renal or ureteral calculus is not as high as previously believed; therefore, the absence of hematuria should not prematurely delete urolithiasis from the differential diagnosis of back, abdominal or groin pain. Physician examination of serial urine specimens collected during maximal pain may increase the detection of hematuria and aid in the diagnosis of urolithiasis.

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Medical Practice Question

EDITOR'S NOTE: *From time to time medical practice questions from organizations with a legitimate interest in the information are referred to the Scientific Board by the Quality Care Review Commission of the California Medical Association. The opinions offered are based on training, experience and literature reviewed by specialists. These opinions are, however, informational only and should not be interpreted as directives, instructions or policy statements.*

Biochemical Biopsy

QUESTION:

Is biochemical biopsy considered accepted medical practice?

OPINION:

In the absence of a specific clinical context and guidance by informed clinical judgment, it is the opinion of the Scientific Advisory Panel on Pathology that the value of such an extensive battery of laboratory tests as offered by biochemical biopsy is unknown. Biochemical biopsy involves a complex series of blood tests, the results of which are then analyzed by computer in an attempt to establish a diagnosis. Patients recommended for this procedure include those with vague patterns of symptomatology and no evident primary disease pattern, those not responding to therapies because of some secondary subclinical condition and those who cannot communicate their symptoms or complaints.

Computer analysis of laboratory data is accepted practice. It can shorten diagnostic time and can greatly assist clinicians both in diagnosis and treatment. The method proposed by the biochemical biopsy, however, suffers from blind overkill. Though most of the tests cited are valid and may give additional direction when used with discretion and ordered on the basis of clinical findings, other tests listed would be done at unnecessary expense. Occasionally, unsuspected pathologic conditions may be suggested by "blind" laboratory studies, but just as frequently misdirection may be the result. The accuracy and reliability of this method remain to be documented and its expense proved cost-effective.

In Memoriam

California Medical Association

ASHLEY, FRANKLIN L., Los Angeles. Died February 14, 1985, in St Petersburg, Florida, of cancer, aged 69. Graduate of Northwestern University Medical School, Chicago, 1941. Licensed in California in 1947. Dr Ashley was a member of the Los Angeles County Medical Association.

BROWN, JOHN W., Sacramento. Died February 26, 1985, aged 74. Graduate of the University of California Medical School, Berkeley-San Francisco, 1935. Licensed in California in 1935. Dr Brown was a retired member of the Alameda-Contra Costa Medical Association.

DUBILIER, WILLIAM, San Francisco. Died January 30, 1985, in Tiburon, aged 60. Graduate of Cornell University Medical College, New York, 1948. Licensed in California in 1958. Dr Dubilier was a member of the San Francisco Medical Society.

IMES, CLIFFORD H., Vallejo. Died February 2, 1985, in Sacramento of injuries received in automobile accident, aged 62. Graduate of the College of Medical Evangelists, Loma Linda-Los Angeles, 1950. Licensed in California in 1950. Dr Imes was a member of the Napa County Medical Society.

LORENZ, HERMANN E., Sacramento. Died February 15, 1985, in Sacramento of myocardial infarction, aged 82. Graduate of St Louis University School of Medicine, St Louis, 1929. Licensed in California in 1929. Dr Lorenz was a member of the Sacramento-El Dorado Medical Society.

REICH, AUGUST, San Francisco. Died March 17, 1985, in Woodland, aged 80. Graduate of Stanford University School of Medicine, Palo-Alto-San Francisco, 1932. Licensed in California in 1932. Dr Reich was a retired member of the San Francisco Medical Society.

TAYLOR, JAMES MELVIN, Fresno. Died January 27, 1985, aged 76. Graduate of Baylor University College of Medicine, Houston, 1936. Licensed in California in 1936. Dr Taylor was a retired member of the Fresno-Madera Medical Society.

WILLETT, FORREST M., San Francisco. Died December 9, 1984, in San Mateo, aged 80. Graduate of Stanford University School of Medicine, Palo Alto-San Francisco, 1939. Licensed in California in 1939. Dr Willett was a retired member of the San Francisco Medical Society.

WILSON, ROGER, San Francisco. Died February 21, 1985, in Visalia of kidney disease, aged 64. Graduate of the University of Cambridge Faculty of Medicine, Cambridge, 1947. Licensed in California in 1952. Dr Wilson was an associate member of the San Francisco Medical Society.

New Mexico Medical Society

MILLICAN, EDITH F., Las Vegas, New Mexico. Died February 14, 1985, aged 70. Graduate of Medical College of Pennsylvania, Philadelphia, 1939. Licensed in New Mexico in 1942. Dr Millican was an emeritus member of the San Miguel County Medical Society.

Utah State Medical Association

BIRD, MYRON EVANS, Delta. Died December 30, 1984, in Provo, aged 88. Graduate of the University of Illinois College of Medicine, Chicago, 1928. Licensed in Utah in 1928. Dr Bird was a member of the Utah County Medical Society.

CLEGG, REED S., Salt Lake City. Died February 16, 1985, in Salt Lake City, aged 72. Graduate of Northwestern University Medical School, Chicago, 1937. Licensed in Utah in 1946. Dr Clegg was a member of the Salt Lake County Medical Society.

THOMSON, WENDELL, J., Ogden. Died December 8, 1984, in Ogden, aged 85. Graduate of Columbia University College of Physicians and Surgeons, New York, 1932. Licensed in Utah in 1935. Dr Thomson was a member of the Weber County Medical Society.

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2. Pool PE, Seagren SC, Bonanno JA, et al: The treatment of exercise-inducible chronic stable angina with diltiazem: Effect on treadmill exercise. Chest 78 (July suppl):234-238, 1980.

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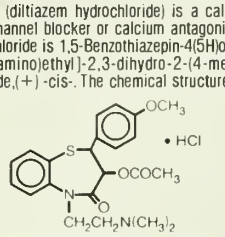
DESCRIPTION

CARDIZEM® (diltiazem hydrochloride) is a calcium ion influx inhibitor (slow channel blocker or calcium antagonist). Chemically, diltiazem hydrochloride is 1,5-Benzothiazepin-4(5H)one,3-(acetyloxy) -5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-, monohydrochloride,(+) -cis-. The chemical structure is:



Diltiazem hydrochloride is a white to off-white crystalline powder with a bitter taste. It is soluble in water, methanol, and chloroform. It has a molecular weight of 450.98. Each tablet of CARDIZEM contains either 30 mg or 60 mg diltiazem hydrochloride for oral administration.

CLINICAL PHARMACOLOGY

The therapeutic benefits achieved with CARDIZEM are believed to be related to its ability to inhibit the influx of calcium ions during membrane depolarization of cardiac and vascular smooth muscle.

Mechanisms of Action. Although precise mechanisms of its antianginal actions are still being delineated, CARDIZEM is believed to act in the following ways:

1. Angina Due to Coronary Artery Spasm: CARDIZEM has been shown to be a potent dilator of coronary arteries both epicardial and subendocardial. Spontaneous and ergonovine-induced coronary artery spasm are inhibited by CARDIZEM.
2. Exertional Angina: CARDIZEM has been shown to produce increases in exercise tolerance, probably due to its ability to reduce myocardial oxygen demand. This is accomplished via reductions in heart rate and systemic blood pressure at submaximal and maximal exercise work loads.

In animal models, diltiazem interferes with the slow inward (depolarizing) current in excitable tissue. It causes excitation-contraction uncoupling in various myocardial tissues without changes in the configuration of the action potential. Diltiazem produces relaxation of coronary vascular smooth muscle and dilation of both large and small coronary arteries at drug levels which cause little or no negative inotropic effect. The resultant increases in coronary blood flow (epicardial and subendocardial) occur in ischemic and nonischemic models and are accompanied by dose-dependent decreases in systemic blood pressure and decreases in peripheral resistance.

Hemodynamic and Electrophysiologic Effects. Like other calcium antagonists, diltiazem decreases sinoatrial and atrioventricular conduction in isolated tissues and has a negative inotropic effect in isolated preparations. In the intact animal, prolongation of the AH interval can be seen at higher doses.

In man, diltiazem prevents spontaneous and ergonovine-provoked coronary artery spasm. It causes a decrease in peripheral vascular resistance and a modest fall in blood pressure and, in exercise tolerance studies in patients with ischemic heart disease, reduces the heart rate-blood pressure product for any given work load. Studies to date, primarily in patients with good ventricular function, have not revealed evidence of a negative inotropic effect; cardiac output, ejection fraction, and left ventricular end diastolic pressure have not been affected. There are as yet few data on the interaction of diltiazem and beta-blockers. Resting heart rate is usually unchanged or slightly reduced by diltiazem.

Intravenous diltiazem in doses of 20 mg prolongs AH conduction time and AV node functional and effective refractory periods approximately 20%. In a study involving single oral doses of 300 mg of CARDIZEM in six normal volunteers, the average maximum PR prolongation was 14% with no instances of greater than first-degree AV block. Diltiazem-associated prolongation of the AH interval is not more pronounced in patients with first-degree heart block. In patients with sick sinus syndrome, diltiazem significantly prolongs sinus cycle length (up to 50% in some cases).

Chronic oral administration of CARDIZEM in doses of up to 240 mg/day has resulted in small increases in PR interval, but has not usually produced abnormal prolongation. There were, however, three instances of second-degree AV block and one instance of third-degree AV block in a group of 959 chronically treated patients.

Pharmacokinetics and Metabolism. Diltiazem is absorbed from the tablet formulation to about 80% of a reference capsule and is subject to an extensive first-pass effect, giving an absolute bioavailability (compared to intravenous dosing) of about 40%. CARDIZEM undergoes extensive hepatic metabolism in which 2% to 4% of the unchanged drug appears in the urine. In vitro binding studies show CARDIZEM is 70% to 80% bound to plasma proteins. Competitive ligand binding studies have also shown CARDIZEM binding is not altered by therapeutic concentrations of digoxin, hydrochlorothiazide, phenylbutazone, propranolol, salicylic acid, or warfarin. Single oral doses of 30 to 120 mg of CARDIZEM result in detectable plasma levels within 30 to 60 minutes and peak plasma levels two to three hours after drug administration. The plasma elimination half-life following single or multiple drug administration is approximately 3.5 hours. Desacetyl diltiazem is also present in the plasma at levels of 10% to 20% of the parent drug and is 25% to 50% as potent a coronary vasodilator as diltiazem. Therapeutic blood levels of CARDIZEM appear to be in the range of 50 to 200 ng/ml. There is a departure from dose-linearity when single doses above 60 mg are given; a 120-mg dose gave blood levels three times that of the 60-mg dose. There is no information about the effect of renal or hepatic impairment on excretion or metabolism of diltiazem.

INDICATIONS AND USAGE

1. **Angina Pectoris Due to Coronary Artery Spasm.** CARDIZEM is indicated in the treatment of angina pectoris due to coronary artery spasm. CARDIZEM has been shown effective in the treatment of spontaneous coronary artery spasm presenting as Prinzmetal's variant angina (resting angina with ST-segment elevation occurring during attacks).
2. **Chronic Stable Angina (Classic Effort-Associated Angina).** CARDIZEM is indicated in the management of chronic stable angina. CARDIZEM has been effective in controlled trials in reducing angina frequency and increasing exercise tolerance.

There are no controlled studies of the effectiveness of the concomitant use of diltiazem and beta-blockers or of the safety of this combination in patients with impaired ventricular function or conduction abnormalities.

CONTRAINDICATIONS

CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker, and (3) patients with hypotension (less than 90 mm Hg systolic).

WARNINGS

1. **Cardiac Conduction.** CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (six of 1243 patients for 0.48%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.
2. **Congestive Heart Failure.** Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). Experience with the use of CARDIZEM alone or in combination with beta-blockers in patients with impaired ventricular function is very limited. Caution should be exercised when using the drug in such patients.
3. **Hypotension.** Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.
4. **Acute Hepatic Injury.** In rare instances, patients receiving CARDIZEM have exhibited reversible acute hepatic injury as evidenced by moderate to extreme elevations of liver enzymes. (See PRECAUTIONS and ADVERSE REACTIONS.)

PRECAUTIONS

General. CARDIZEM (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any new drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Drug Interaction. Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS).

Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers or digitalis is usually well tolerated. Available data are not sufficient, however, to predict the effects of concomitant treatment, particularly in patients with left ventricular dysfunction or cardiac conduction abnormalities. In healthy volunteers, diltiazem has been shown to increase serum digoxin levels up to 20%.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response in in vitro bacterial tests. No intrinsic effect on fertility was observed in rats.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

There are no well-controlled studies in pregnant women; therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when CARDIZEM is administered to a nursing woman if the drug's benefits are thought to outweigh its potential risks in this situation.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded.

In domestic placebo-controlled trials, the incidence of adverse reactions reported during CARDIZEM therapy was not greater than that reported during placebo therapy.

The following represent occurrences observed in clinical studies which can be at least reasonably associated with the pharmacology of calcium influx inhibition. In many cases, the relationship to CARDIZEM has not been established. The most common occurrences, as well as their frequency of presentation, are: edema (2.4%), headache (2.1%), nausea (1.9%), dizziness (1.5%), rash (1.3%), asthenia (1.2%), AV block (1.1%). In addition, the following events were reported infrequently (less than 1%) with the order of presentation corresponding to the relative frequency of occurrence.

Cardiovascular:	Flushing, arrhythmia, hypotension, bradycardia, palpitations, congestive heart failure, syncope.
Nervous System:	Paresthesia, nervousness, somnolence, tremor, insomnia, hallucinations, and amnesia.
Gastrointestinal:	Constipation, dyspepsia, diarrhea, vomiting, mild elevations of alkaline phosphatase, SGOT, SGPT, and LDH.
Dermatologic:	Pruritus, petechiae, urticaria, photosensitivity.
Other:	Polyuria, nocturia.

The following additional experiences have been noted:

A patient with Prinzmetal's angina experiencing episodes of vasospastic angina developed periods of transient asymptomatic asystole approximately five hours after receiving a single 60-mg dose of CARDIZEM.

The following postmarketing events have been reported infrequently in patients receiving CARDIZEM: erythema multiforme; leukopenia; and extreme elevations of alkaline phosphatase, SGOT, SGPT, LDH, and CPK. However, a definitive cause and effect between these events and CARDIZEM therapy is yet to be established.

OVERDOSAGE OR EXAGGERATED RESPONSE

Overdosage experience with oral diltiazem has been limited. Single oral doses of 300 mg of CARDIZEM have been well tolerated by healthy volunteers. In the event of overdosage or exaggerated response, appropriate supportive measures should be employed in addition to gastric lavage. The following measures may be considered:

Bradycardia	Administer atropine (0.60 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.
High-Degree AV Block	Treat as for bradycardia above. Fixed high-degree AV block should be treated with cardiac pacing.
Cardiac Failure	Administer inotropic agents (isoproterenol, dopamine, or dobutamine) and diuretics.
Hypotension	Vasopressors (eg, dopamine or levarterenol bitartrate).

Actual treatment and dosage should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

The oral LD_{50}'s in mice and rats range from 415 to 740 mg/kg and from 560 to 810 mg/kg, respectively. The intravenous LD_{50}'s in these species were 60 and 38 mg/kg, respectively. The oral LD_{50} in dogs is considered to be in excess of 50 mg/kg, while lethality was seen in monkeys at 360 mg/kg. The toxic dose in man is not known, but blood levels in excess of 800 ng/ml have not been associated with toxicity.

DOSAGE AND ADMINISTRATION

Exertional Angina Pectoris Due to Atherosclerotic Coronary Artery Disease or Angina Pectoris at Rest Due to Coronary Artery Spasm. Dosage must be adjusted to each patient's needs. Starting with 30 mg four times daily, before meals and at bedtime, dosage should be increased gradually (given in divided doses three or four times daily) at one- to two-day intervals until optimum response is obtained. Although individual patients may respond to any dosage level, the average optimum dosage range appears to be 180 to 240 mg/day. There are no available data concerning dosage requirements in patients with impaired renal or hepatic function. If the drug must be used in such patients, titration should be carried out with particular caution.

Concomitant Use With Other Antianginal Agents:

1. **Sublingual NTG** may be taken as required to abort acute anginal attacks during CARDIZEM therapy.
2. **Prophylactic Nitrate Therapy**—CARDIZEM may be safely coadministered with short- and long-acting nitrates, but there have been no controlled studies to evaluate the antianginal effectiveness of this combination.
3. **Beta-blockers.** (See WARNINGS and PRECAUTIONS.)

HOW SUPPLIED

Cardizem 30-mg tablets are supplied in bottles of 100 (NDC 0088-1771-47) and in Unit Dose Identification Paks of 100 (NDC 0088-1771-49). Each green tablet is engraved with MARION on one side and 1771 engraved on the other. CARDIZEM 60-mg scored tablets are supplied in bottles of 100 (NDC 0088-1772-47) and in Unit Dose Identification Paks of 100 (NDC 0088-1772-49). Each yellow tablet is engraved with MARION on one side and 1772 on the other.

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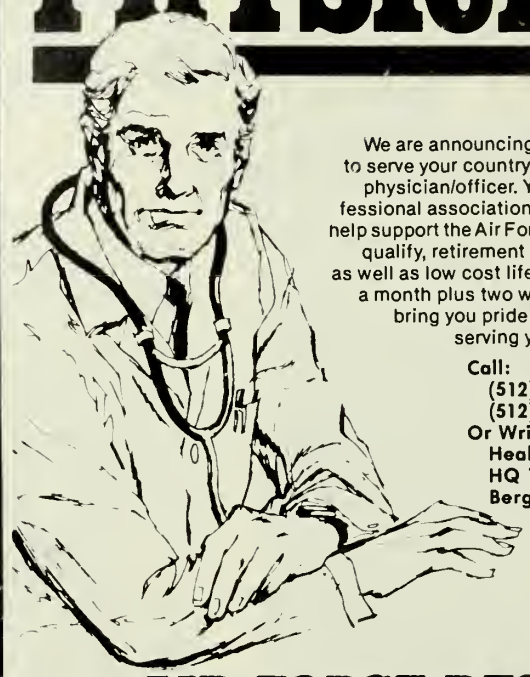

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CONTINUING MEDICAL EDUCATION

(Continued from Page 631)

Wednesday-Sunday. 17 hrs. Contact: Northern California Psychotherapy Society, 188 Gravatt Drive, Berkeley 94705.

June 6-7—**Occupational and Env. Medical Symposium.** UC, Davis at Beverly Garland Hotel, Sacramento. Thursday-Friday.

June 14-16—**29th Annual Postgraduate Symposium Update 1985.** San Diego Academy of Family Physicians at Hotel Del Coronado, Coronado. Friday-Sunay. Contact: San Diego Acad. of Family Physicians, 2834 Levante St., La Costa 92008. (619) 436-0981.

June 17-22—**The UCI Family Practice Refresher Course.** UCI at Westin South Coast Plaza, Long Beach. Monday-Saturday. 58 hrs.

June 22-23—**Mullens-White Symposia: Non-Invasive Evaluation and Minimal Incision Surgery.** Stanford at Palo Alto. Saturday-Sunday.

June 29-30—**7th Annual Symposium on Toxicological Emergencies.** UCSF at Cathedral Hill Hotel, San Francisco. Saturday-Sunday. Fee: $210.

June 30—**Personality and Disease: The Emerging Field of Psychoneuro-immunology.** UCSD at University of California, Santa Barbara. Sunday. 6 hrs.

July 5-7—**6th Annual Symposium: Laboratory & Clinical Aspects of Microbiological Diagnosis.** UCLA at Hotel Del Coronado, Coronado. Friday-Sunday. Fee: $175.

July 8-11—**Family Practice Board Review Course.** UCSF. Monday-Thursday.

ALASKA

June 5-8—**Alaska State Medical Association Convention.** Haines. Wednesday-Saturday. Contact: ASMA, 4107 Laurel St., Anchorage 99504. (907) 562-2662.

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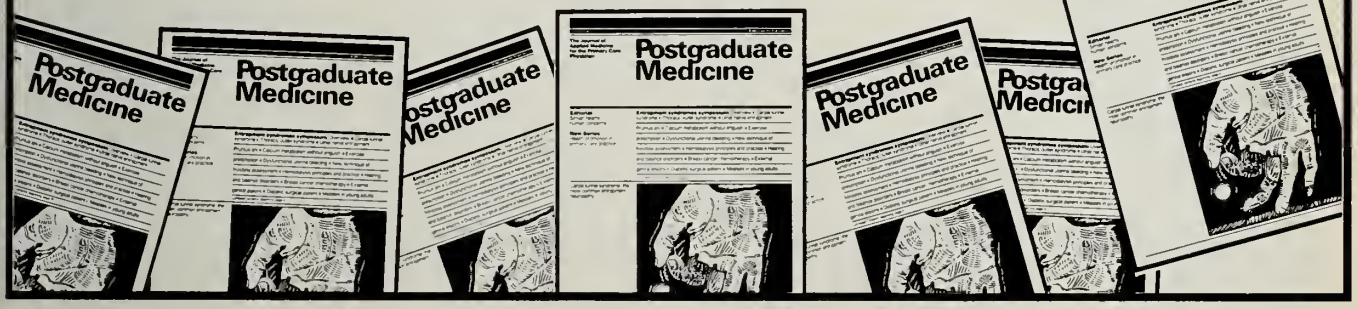

CONTINUING MEDICAL EDUCATION

IDAHO

July 24-27—**Idaho Medical Association Annual Meeting.** Sun Valley. Wednesday-Saturday. Contact: IMA, PO Box 2668, Boise 83701. (208) 344-7888.

MONTANA

May 22-24—**Internal Medicine Review.** University of Washington at Great Falls, Billings, Missoula. Wednesday-Friday. Contact: U/W School of Medicine, Div. of CME-50, Seattle, WA 98195. (206) 543-1050.

NEW MEXICO

Information, requests for accreditation and items to be listed should be sent to the chairman of the CME Committee, New Mexico Medical Society, 303 San Mateo NE, Suite 204, Albuquerque, NM 87108 at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 266-7868.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

May 16-18—**UNM Neurology '85: New Approaches to Common Problems.** Albuquerque. Thursday-Saturday. AMFAC Hotel. AMA Cat. I. Contact: Office of CME, UNM SOM, Albuquerque 87131. (505) 277-3942.

May 31-June 1—**Cancer Update '85.** Albuquerque. Friday-Saturday. AMFAC Hotel. AMA Cat. I. Contact: Office of CME, UNM SOM, Albuquerque 87131. (505) 277-3942.

(Continued on Page 728)

INFORMATION FOR AUTHORS

Submitting Manuscripts

Manuscripts for consideration should be sent to the editor, Malcolm S. M. Watts, MD, 44 Gough Street, San Francisco, California 94103. The transmittal letter should designate one person as correspondent and include complete address, with ZIP code and telephone number.

In view of *The Copyright Revision Act of 1976,* transmittal letters should contain the following language: "In consideration for reviewing and editing my submission, the author(s) undersigned hereby transfers, assigns or otherwise conveys all copyright ownership to THE WESTERN JOURNAL OF MEDICINE in the event that such work is published by the journal." This statement should be signed by *all* the authors.

Authors are urged to seek clarity and succinctness in all manuscripts regardless of subject matter or format and to give close attention to syntax, grammar and spelling.

Clinical Investigation Section

Articles that authors wish to have considered for the Clinical Investigation section should be so designated in the transmittal letter. The type of articles appropriate for this section are those that describe experimental work in humans that extensively and prospectively examines scientific hypotheses relating to disease. An article describing a single case report will not normally be considered appropriate for this section.

Preparing Manuscripts

The original manuscript and *two* copies should be submitted on heavy bond paper (8½ by 11 inches, *not* erasable), typed *double-spaced throughout* (including legends, tables and references) on one side of the paper, with 1½-inch margins. Ordinarily, articles should not exceed 3,000 words (less than 15 text pages, typed double-spaced). Under exceptional circumstances only will articles longer than 4,000 words be published. Pages should be numbered consecutively, beginning with the title page.

Style

Abbreviations. Use of abbreviations should be minimized. If they are necessary, abbreviations should be spelled out at first mention, with the abbreviation itself immediately following in parentheses.

Weights and measures. All measurements should be given in metric units. English equivalents should be given parenthetically if the measurements were originally done in English units.

Temperatures. Temperature readings should be given first in Celsius, followed by the Fahrenheit equivalent in parentheses.

Drug names. If the trade name of a drug is used, the generic name should be given first, followed by the trade name in parentheses. Trade names are capitalized, generic names are not.

Title Page

Titles are best when brief and concise. The title page should include the full name of the author(s), with degrees, academic or professional titles, complete addresses and any institutional or other affiliations. The complete name and address of the person who will handle reprint requests also should appear on this page.

Abstract

The abstract (approximately 150 words) should be a short summary, saying in brief what is said at length in the body of the article—rather than such and such "is discussed," "is presented" or "was investigated."

Tables and Figures

Tables

Each table should be typed on a separate sheet of paper, be numbered consecutively in Arabic numerals, have a brief descriptive title and have its position indicated in the text.

Illustrations (Figures)

Three sets of clear, unmounted black and white glossy prints of figures should be submitted (preferably 5 by 7 inches, but no larger than 8½ by 11 inches). For line drawings, original artwork or glossy prints are acceptable. Illustrations should be numbered consecutively in Arabic numerals and their position indicated in the text. Figure number, first author's name and top of the photo should be shown on the reverse side of each illustration. Recognizable photographs of patients are to be masked and written permission for publication obtained from the patients.

Legends

All legends for figures should be typed together on a separate sheet of paper. Magnification and stain for photomicrographs should be indicated in parentheses.

Permission for Reproduction

If an illustration or table has been used previously in another publication, written permission for its use must be obtained from the publisher, and should accompany the manuscript. The source should be acknowledged in the legend if it can be done briefly by citation of a reference number. Otherwise, acknowledgment is made at the end of the figure legend or at the bottom of the table.

References

References should be limited to those cited in the text. They must be typed double-spaced and numbered consecutively as they appear in the manuscript. (See examples below for style.) Abbreviations of journal titles should conform to those used in *Index Medicus.*

Journal Articles

Note handling of multiple authorship. If more than three authors are listed as contributors, use "et al" to designate those names after the first three. Also note capitalization, punctuation, mention of inclusive page numbers and year of publication. Separate the subtitle from the title by either a dash or a colon. Use colon *only* if it appears in the original citation.

1. Jones JS, Anderson HW, Johnson DW, et al: The athletic heart revisited—Sudden death of a 28-year-old athlete. JAMA 1978; 292:444-456

2. Graybill JR, Alford RH, Smith RG, et al: Cell-mediated immunity in cryptococcosis: A brief review. Cell Immunol 1978; 7:76-79

Books

Note handling of "edition," "editor(s)," and "volume," as well as appropriate sequence of reference information and capitalization of chapters and titles.

3. Berne EJ, Smith TL: Role playing in therapy, chap 2, Principles of Group Therapy. New York, Oxford University Press, 1966, pp 35-51 *(author of chapter same as author of book)*

4. Munsung JM: The role of drugs, chap 2, *In* Brest AN, Mayer JH (Eds): Hypertension—Vol 2, Therapy, 2nd Ed. Springfield, Ill, Charles C Thomas, 1961, pp 456-479 *(author of chapter different from authors of book)*

Pamphlets, Monographs or Books With No Given Author

5. AMA Department of Drugs: AMA Drug Evaluation, 3rd Ed. Littleton, Mass, Publishing Sciences Group, 1977 *(corporate author)*

6. Compilation of Standard Definitions, 3rd Ed. Philadelphia, American Society for Testing and Materials, 1976 *(no given author; give name and place of publisher)*

Articles in Press or Accepted for Publication

Any article accepted for publication should include the name of the journal (appropriately abbreviated) in which it will appear, and the phrase "in press" or "accepted for publication" in place of the date of publication.

Personal Communications and Unpublished Data

This information should *not* be included in the reference list but should be given in parentheses in the body of the text. Date of communication, whether it was personal or written, and the person's name, highest academic degree and professional affiliation should be provided.

Acknowledgments

It is the policy of the *WJM* not to print acknowledgments, the feeling being that if a person has contributed enough to a paper to be mentioned, he or she should be included among the authors, or the contribution should be mentioned in the body of the paper or in a footnote.

Correspondence

Brief manuscripts commenting on articles that have appeared in the journal, containing information of interest to physicians or discussing issues of the day will be considered for publication. Very short reports of cases, clinical experience, clinical studies, adverse effects and the like also will be considered. Items for the Correspondence section should not exceed 600 words and should have no more than five bibliographic references and one figure or table.

Author Responsibility

Authors are responsible for all statements made in articles. Manuscripts are considered for publication with the explicit understanding that they are original, have not been published previously and are not simultaneously under consideration by any other publication.

All accepted manuscripts are subject to copy editing, and authors are sent edited galleys for approval. No changes will be made after the final, edited version has been approved by the author.

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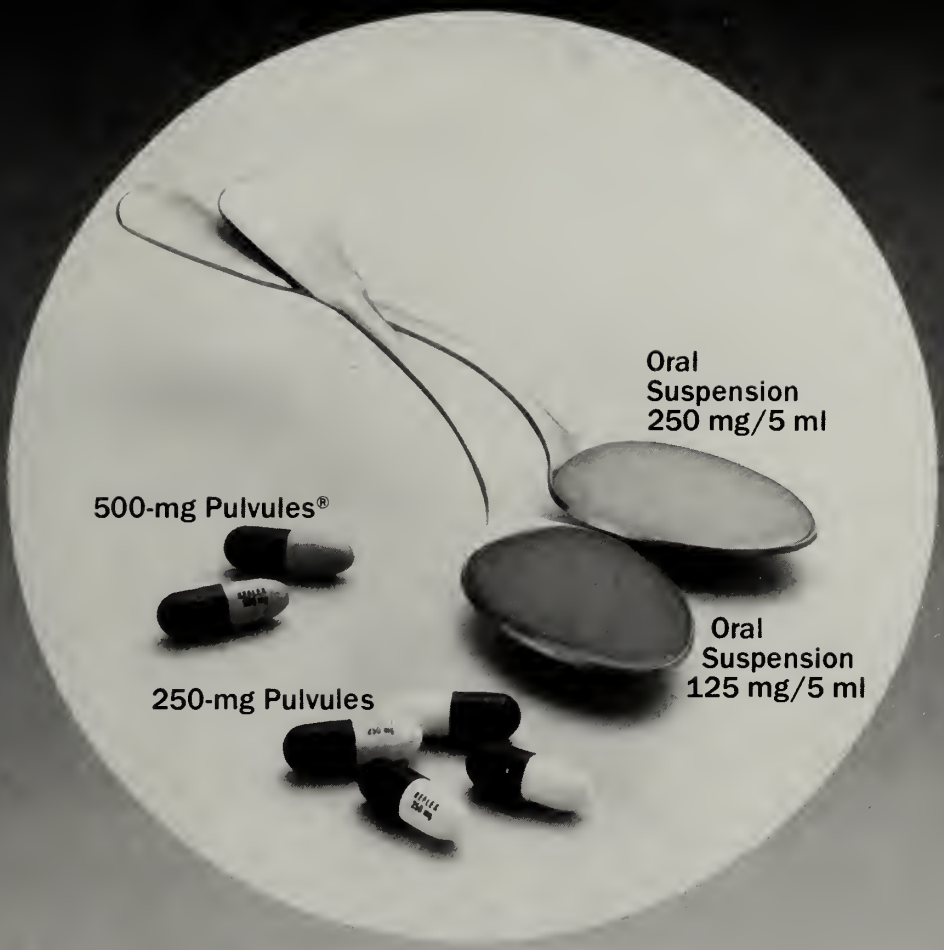

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(Continued from Page 725)

June 1-9—**The Body in Analysis.** Abiquiu. Saturday-Sunday. The Ghost Ranch. 36 hrs. NM Category I. Contact: Secretary, Ghost Ranch Conference, PO Box 417, Wilmette, IL 60091. (312) 256-7551.

June 11-14—**Medicolegal Investigation of Death.** Albuquerque. Tuesday-Friday. AMA Cat. I. AMFAC Hotel. Contact: Office of CME, UNM SOM, Albuquerque 87131. (505) 277-3942.

July 11-13—**General Surgical Update.** Albuquerque. Thursday-Saturday. Marriott Hotel. AMA Cat. I. Contact: Office of CME, UNM SOM, Albuquerque 87131. (505) 277-3942.

July 11-13—**Annual Meeting—New Mexico Ophthalmological Society.** Santa Fe. Thursday-Saturday. Hilton Inn. 8½ hrs. AMA Cat. I. Contact: John M. Mezoff, MD, 508 Cabezon Court, Gallup 87301.

July 15-18—**28th Annual Ruidoso Family Practice Seminar.** Mescalero. Monday-Thursday. Inn of the Mountain Gods. 20 hrs. AMA Cat. I and AAFP Prescribed Credit. Contact: NM Chapter, AAFP, PO Box 23070, Albuquerque 87192. (505) 298-5300.

OREGON

The following list of continuing medical offerings in the state of Oregon is compiled by the Oregon Medical Association's Council on Medical Education. If you wish to submit information regarding future postgraduate courses, please submit the information to James A. Kronenberg, Associate Executive Director, Oregon Medical Association, 5210 SW Corbett Ave., Portland, OR 97201, or phone (503) 226-1555.

MEDICAL GRAND ROUNDS

Douglas Community Hospital, 738 West Harvard Avenue, Roseburg 97470:

Every Monday, 12:30 p.m. Contact: Robert A. Driver, MD, Douglas Community Hospital, 738 West Harvard Avenue, Roseburg, OR 97470. (503) 673-6641.

Emanuel Hospital, 2801 N. Gantenbein Street, Portland 97227:

Every Friday, 8:00 a.m. to 9:00 a.m. **Medical Grand Rounds.** Contact: Philipa McClure, Emanuel Hospital, 2801 N. Gantenbein Street, Portland, OR 92227. (505) 280-3200.

CONTACT INFORMATION

OHSU-CME—Contact: Division of Continuing Medical Education, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8700.

Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland 97210:

Every Wednesday, 8:00 a.m. to 9:00 a.m. **Medicine Grand Rounds.** Nursing Education Building, Room 110. Contact: Department of Medicine, Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland, OR 97201. (503) 229-7454.

Providence Medical Center, 4805 NE Glisan, Portland 97213:

Every Wednesday, 8:00 a.m. **Medical Grand Rounds.** Contact: Richard Wernick, MD, Providence Medical Center, 4805 NE Glisan, Portland, OR 97213. (503) 230-6085.

Sacred Heart General Hospital, 1200 Alder Street, Eugene, OR 97440:

Every Tuesday, 8:00 a.m. to 9:00 a.m. **Medical Grand Rounds.** Hospital Auditorium. Contact: Medical Education Committee. PO Box 10905, Eugene, OR 97440.

Salem Hospital, 665 Winter Street SE, Salem 97301:

First and third Thursday of each month 7:15 a.m. to 8:15 a.m. **Medical Live Audit Conference.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter Street SE, Salem, OR 97301. (503) 370-5339.

Every Friday, 7:30 a.m. to 8:30 a.m. **Friday Grand Rounds.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter Street SE, Salem, OR 97301. (503) 370-5339.

St. Vincent Hospital & Medical Center, 9205 SW Barnes Road, Portland 97225:

First, third, fourth and fifth Wednesday of each month, 8:00 a.m. to 9:00 a.m. **Medical Grand Rounds.** Souther Auditorium. Contact: Bonnie Conger, Secretary to Dr Kenneth Melvin, St. Vincent Hospital & Medical Center, 9205 SW Barnes Road, Portland 97225. (503) 297-4411, Ext. 2230

Oregon Health Sciences University, Department of Psychiatry, Portland 97201:

Every Wednesday, 4:00 p.m. to 5:00 p.m. **Department of Psychiatry Grand Round Presentations.** Room 8B-60, University Hospital South, Oregon Health Sciences University. Contact: Dept. of Psychiatry, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8144.

Oregon Health Sciences University, Department of Medicine, Portland 97201:

Every Tuesday, 8:00 a.m. to 9:00 a.m. **Department of Medicine Grand Rounds.** U.H.S.-8B-60, Or-

egon Health Sciences University. Contact: Dept. of Medicine, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8607.

FAMILY PRACTICE GRAND ROUNDS

Every Wednesday, 11:00 a.m. to 12:00 Noon. **Family Practice Grand Rounds.** Family Practice Center, Oregon Health Sciences University, Portland. Contact: William A. Fisher, MD, Oregon Health Sciences University, Department of Family Practice, Portland, OR 97201. (503) 225-7590.

INTERNAL MEDICINE

May 31-June 1—**Internal Medicine Update.** Portland. Friday-Saturday. Marriott Hotel. Contact: OHSU-CME.

OF INTEREST TO ALL PHYSICIANS

May 17—**Infectious Diseases in Clinical Practice.** Portland. Friday. OHSU Library Auditorium. Contact: OHSU-CME.

May 31-June 1—**Internal Medicine Update.** Portland. Friday-Saturday. Marriott Hotel. Contact: OHSU-CME.

June 28—**Osteoporosis Conference.** Portland. Friday. Red Lion Lloyd Center. Contact: OHSU-CME.

September 6-7—**Ashland Conference: Infectious Disease.** Ashland. Friday-Saturday. Ashland Hills Inn. Contact: OHSU-CME.

October 4-5—**Fifth Annual Toxicology Conference.** Portland. Friday-Saturday. Marriott Hotel. Contact: OHSU-CME.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah State Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. They also must meet the definition of Utah Approved CME Credit for the purpose of medical license reregistration in Utah. Accredited institutions wishing to list AMA Category 1/Utah Approved CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, Utah 84102; or phone (801) 355-5290. For information on CME accreditation or on the CME requirements of the Utah Physicians' Licensing Board, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution or the CME office for current details.

MEDICAL GRAND ROUNDS

Each Wednesday—8:00-9:00 a.m. Alternating between University of Utah Medical Center and VA Medical Center, Salt Lake City. Contact: William D. Odell, MD, PhD, Professor and Chairman, Dept. of Internal Medicine, Univ. of Utah, (801) 581-7606.

* * *

June 7-8—**Advanced Trauma Life Support** (Sponsor: University of Utah). Friday-Saturday. Salt Lake Quality Inn, Salt Lake City. 16 hrs. $405. Contact: Kim Tanner, RN, (801) 533-6608.

July 14-19—**Summer Update in Clinical Microbiology and Immunology** (Sponsor: University of Utah). Sunday-Friday. Jackson Hole, American Snow King. 23 hrs. Contact: John Matsen, MD, (801) 581-7480.

SPONSORS OF COURSES—ABBREVIATIONS

AF: Arthritis Foundation, 1174 East 2700 South, Salt Lake City 84117. (801) 466-9389.

CH: Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price, UT 84501. (801) 637-4800.

CWH: Cottonwood Hospital, 5770 South 300 East, Salt Lake City 84101. (801) 262-3461.

FHP: Family Health Program/Utah, 323 South Sixth East, Salt Lake City 84102. (801) 335-1234. Contact: Kay Schultz for course information.

HAFB: Hill Air Force Hospital, Hill Air Force Base 84406. (801) 777-1262.

HCH: Holy Cross Hospital, 1045 East First South, Salt Lake City 84102. (801) 350-4744.

LDSH: Latter-Day Saints Hospital, 325 8th Avenue, Salt Lake City 84143, (801) 350-1100.

MDH: McKay-Dee Hospital Center, 3939 Harrison Blvd., Ogden 84409. (801) 399-4141.

OEH: Rocky Mountain Center for Occupational and Environmental Health, 50 North Medical Drive, Salt Lake City 84132. (801) 581-8719.

OSS: Ogden Surgical Society, PO Box 9311, Ogden 84409.

PCMC: Primary Children's Medical Center, 320 12th Ave., Salt Lake City 84103. (801) 363-1221.

SHCC: Shriners Hospital for Crippled Children, Intermountain Unit, Fairfax Ave. at Virginia St., Salt Lake City 84103. (801) 532-5307.

SLSC: Salt Lake Surgical Center, 617 East 3900 South, Salt Lake City 84117. (801) 261-3141.

UAFP: Utah Academy of Family Physicians, 1146 Westminster Ave., Salt Lake City 84105. (801) 466-9478.

UUMC: University of Utah Medical Center, 50 North Medical Drive, Salt Lake City 84132. (801) 581-2258.

USMA: Utah State Medical Association, 540 East Fifth South, Salt Lake City 84102. (801) 355-7477.

UVH: Utah Valley Hospital, 1034 North Fifth West, Provo 84601. (801) 373-7850.

VAMC: Veterans Administration Medical Center, 500 Foothill Drive, Salt Lake City 84148. (801) 582-1565.

WASHINGTON

This listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121; or phone (206) 623-4801.

Brochures and Registration Forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

May 17—**Riverton Hospital Lectures.** Seattle. Friday. Riverton Hospital. Contact: U/W.

May 18—**Microcomputers in Rehab Medicine.** Seattle. Saturday. Contact: U/W.

May 21—**Using Pulmonary Function Tests.** Seattle. Tuesday. Ballard Hospital. Contact: U/W.

May 22-24—(MONTANA) **Internal Medicine Review.** Great Falls, Billings, Missoula. Wednesday-Friday. Contact: U/W.

May 28—**Travel and Illness.** Auburn. Tuesday. Auburn General Hospital. Contact: U/W.

May 30-31—**Controversies in Cardiovascular Issues.** Seattle. Thursday-Friday. Contact: U/W.

May 30-31—**Mental Health Policy Forum.** Seattle. Thursday-Friday. Westin. Contact: U/W.

May 31—**Riverton Hospital Lectures.** Seattle. Friday. Riverton Hospital. Contact: U/W.

June 3-9—**Practicing the Medicine of the Future—Today!** Seattle. Monday-Sunday. Contact: Kaaren A. Nichols, MD, or Robert A. Anderson, MD, American Holistic Medical Assn., 21616 76th Ave. West, #110, Edmonds, WA 98020. (206) 776-9196.

June 6-7—**Behavioral Medicine.** Seattle. Thursday-Friday. Westin. Contact: U/W.

June 6-8—**Medical Emergencies.** Seattle. Thursday-Saturday. Contact: VMMC.

June 7—**Riverton Hospital Lectures.** Seattle. Friday. Riverton Hospital. Contact: U/W.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

CME PIERCE COUNTY—Contact: Mrs Maxine Bailey, Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 223-6898.

June 13-14—**Ischemic Heart Disease.** Seattle. Thursday-Friday. Westin. Contact: U/W.

June 13-14—**Advances in Internal Medicine.** Seattle. Thursday-Friday. U/W HUB. Contact: U/W.

June 14—**Riverton Hospital Lectures.** Seattle. Friday. Riverton Hospital. Contact: U/W.

June 15—**Contemporary Thoracic Imaging.** Seattle. Saturday. U/W South Campus Center. Contact: U/W.

June 18—**Small Computers in Medicine.** Seattle. Tuesday. Ballard Hospital. Contact: U/W.

June 19-20—**Financial Planning for Physicians.** Victoria, BC. Wednesday-Friday. Empress Hotel. Contact: U/W.

June 21—**Riverton Hospital Lectures.** Seattle. Friday. Riverton Hospital. Contact: U/W.

June 21-22—**Nutrition of Hospitalized Patient.** Vancouver, BC. Saturday-Sunday. Contact: U/W.

June 25—**What's New in Antibiotics.** Auburn. Tuesday. Auburn General Hospital. Contact: U/W.

June 26-29—**(OREGON) Washington State Chapter, American College of Surgeons.** Sun River, Oregon. Wednesday-Saturday. Sun River Resort. Contact: Richard P. Billingham, MD, 801 Broadway, Suite 712, Seattle 98122. (206) 624-2107.

June 28—**Riverton Hospital Lectures.** Seattle. Friday. Riverton Hospital. Contact: U/W.

June 29-July 3 (CALIFORNIA)—**Pacific Coast Oto-Ophthalmological Society Annual Meeting.** San Diego. Saturday-Wednesday. Hotel Del Coronado. Contact: Robert E. Christensen, MD, Exec. Secretary-Treasurer, JSEI-UCLA, 800 Westwood Plaza, Los Angeles, CA 90024. (213) 625-5298.

July 8-10—**Scientific Aspects of Dance/Exercising Women.** Seattle. Monday-Wednesday. Westin. Contact: U/W.

September 28-October 4 (SAN JUAN ISLANDS)—**Effective Management of Common Sports Injuries.** Saturday-Friday. Contact: Epic Medical Expeditions, PO Box 209, Sun Valley, ID 83353. (206) 788-4995.

WYOMING

June 23-26—**Wyoming Medical Society—Annual Meeting.** Jackson Lake Lodge, Moran. Sunday-Wednesday. Contact: WMS, PO Drawer 4009, Cheyenne 82003-4009. ◆

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ACADEMIC GENERAL INTERNISTS, Cardiologist and Endocrinologist, DO—Wanted for full-time faculty positions. Must be Board admissible or certified, interested in teaching medical students and house staff. Good balance between clinical practice and teaching with research opportunities available. Send CV to Victor H. Kaylarian, DO, Department of Medicine, University of Osteopathic Medicine and Health Sciences, 3200 Grand Ave., Des Moines, IA 50312. All inquiries confidential.

ASSISTANT PROFESSOR level with excellent guaranteed salary and benefits. Send CV to Victor H. Kaylarian, DO, Department of Medicine, University of Osteopathic Medicine and Health Sciences, 3200 Grand Ave., Des Moines, IA 50312. All inquiries confidential.

IDAHO: EXCITING FAMILY PRACTICE AND TIME TO ENJOY THE OUTDOORS. Join group of physicians and nurse practitioners serving five rural communities in Southwest Idaho. Includes interesting obstetrics and health education program. Attractive financial package. Contract Robert H. LeBow, MD, MPH, 1515 Third Street North, Nampa, ID 83651 or call (208) 467-4431.

UNIVERSITY OF WYOMING STUDENT HEALTH SERVICE: The Student Health Service has an opening for a full time physician. The physician must be Board certified in Family Practice or Internal Medicine or Pediatrics, and have approved residency training or extensive practice experience. Applicant must be licensed in the State of Wyoming and have at least two years of primary care experience. Physician to join three full time and three part-time physicians to care for 10,000 students on the campus at Laramie, Wyoming. The Student Health Service has its own laboratory, x-ray, pharmacy and limited emergency services. Salary commensurate with qualifications and experience. The University of Wyoming is an Equal Opportunity/Affirmative Action Employer. Send CV to: Dale C. Brentlinger, MD, Director, Student Health Service, University of Wyoming, University Station Box 3068, Laramie, WY 82071.

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PHYSICIANS WANTED

GENERAL INTERNIST, BOARD CERTIFIED/ELIGIBLE: Multispecialty group, university town central Washington, has space and services available on a lease or compensation basis with future partnership if desired. Contact A. J. Grose, MD, Medical Building Associates, PO Box 369, Ellensburg, WA 98926.

PUGET SOUND/WASHINGTON—Interested in establishing practice in area of excellent recreational opportunities and quality lifestyle? The following BC/BE positions are available in multispecialty clinic of 21 physicians: Occupational Medicine, Ob-Gyn, ENT, Gastroenterology, Surgery, Orthopedics, and Urology. Excellent compensation and benefits. Send CV's to: Executive Director, Western Clinic, PO Box 5467, Tacoma, WA 98405.

OB/GYN-WASHINGTON. Expanding physician owned clinic in Edmonds, WA with one OB/GYN and three FP has opening for full- or part-time OB/GYN. We are a progressive clinic with two female physicians on our staff currently. Benefits include health, dental, disability, and life insurance. Send CV to Philip DuBois, MD, 7935 216th St. S.W. Suite E, Edmonds, WA 98020; (206) 775-0681.

WYOMING—ER STAFF POSITION—Emergency Room in Rawlins, WY with moderate volume. Independent contractor status. Malpractice paid. Very flexible schedule. Excellent hunting, fishing, backpacking and skiing in surrounding area. Send Résumé to: Duane Eugene Abels, DO PC, PO Box 1536, Rawlings, WY 82301 or call (307) 324-2221 x115.

PSYCHIATRIST: The University of Wyoming Student Health Service is now interviewing for a psychiatrist to work during Fall, Spring and Summer semesters. Position available Fall 1985, 9½ month position. Candidates must have completed an approved residency and be Board certified in Psychiatry. Candidate will be asked to rotate night call (3 hours) and week-ends (8 hours per day) with primary care physicians. Selected candidate must have demonstrated the ability to work with college age students. Candidate must also demonstrate knowlege and ability to develop innovative mental health care clinics and supervise other mental health providers as well as post graduate students. Candidate must obtain a Wyoming license within six months if not already licensed. Selected candidate will join seven health care providers to care for 10,000 students in Laramie, Wyoming. Salary commensurate with qualifications and experience. The University of Wyoming is an Equal Opportunity/Affirmative Action Employer. Send CV to: Dale C. Brentlinger, MD, Director, Student Health Service, University of Wyoming, University Station Box 3068, Laramie, WY 82071.

PEDIATRICIAN BE/BC—Full Time—to join well-established academically oriented pediatric practice. Send CV to L. M. Holve, MD, Westside Pediatric Medical Group, 2001 Santa Monica Blvd., Suite 690-W, Santa Monica, CA 90404.

INTERNIST needed to join California private practice Internal Medicine group. Excellent opportunity in rapidly growing metro population of 250,000. Close to many recreational and major metropolitan areas. New office with in-house laboratory, radiology, cardiology. Send CV to Box 6466, Western Journal of Medicine, 44 Gough St., San Francisco, CA 94103.

FAMILY PRACTICE PHYSICIAN—for employment in Community Health Center serving rural hispanic population in Northern New Mexico. Practice includes OB, hospital service, and supervision of two PAs. Scenic mountainous area with easy access to campgrounds and ski slopes. Spanish fluency desirable; excellent benefits package. Contact John Glass at (505) 982-5565, or write to Presybterian Medical Services, PO Box 2267, Santa Fe, New Mexico 87504.

(Continued on Page 734)

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(Continued from Page 732)

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GENERAL SURGEONS needed for long-term practice opportunity in Western Washington community within two hours of Seattle-Tacoma. Training and experience in Vascular or Pediatric Surgery desirable. Practice support package possible. Send CV and reference to Nancy Friedrich, The Friedrich Group, 9284 Ferncliff N.E., Bainbridge Island, WA 98110.

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INSTITUTION PHYSICIAN needed to staff the Wyoming State Training School at Lander, Wyoming. We have 420 mentally retarded residents with a 30 bed Health Care Center with a staff of four physicians. Attractive salary and fringe benefits. No overhead. Pleasant surrounding area including an excellent medical group in Lander. If interested, please contact the Personnel Manager, Wyoming State Training School, 8204 State Highway 789, Lander, WY 82520. An Equal Opportunity Employer.

SOUTH DAKOTA: Expanding physician-owned emergency group has opening for full-time career-oriented Emergency Physicians in South Dakota. Excellent benefits including malpractice, disability, health insurance, profit sharing, etc. Flexible work schedules, excellent working and living conditions. Contact Donald Kougl, MD, (307) 632-1436 or send CV to EMP, P.C., PO Box 805, Cheyenne, WY 82003.

WASHINGTON: OB/GYN AND PEDIATRICIANS. Expanding established primary care group seeking two of each in independent association. Suburban/rural area 20 miles North of Seattle. New facilities. Dr Ware, Silverlake Medical Center, 1819 100th Pl South East, Everett, WA 98204; (206) 337-0800.

PHYSICIANS WANTED

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PHYSICIAN, Full-time, Pacific Bell Medical Program. Will require assignments in San Ramon, Oakland, or San Jose. Highly competitive benefit/salary package. Send CV to A. S. Maida, MD, 817 The Alameda, San Jose, CA 95126.

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ENT PHYSICIAN—General ENT physician with some primary facial surgery and reconstructive experience. Will be joining ENT Group in well established prepaid health plan, located in Southern California. Guaranteed salary and benefits to start. Board certification or eligibility required. For information, call Luann Ellis, toll-free at 1 (800) 446-2255, in California call 1 (800) 336-2255. FHP Professional Staffing, 400 Oceangate Blvd., Suite 1317, Long Beach, CA 90802. For opportunities in Utah, call Maryalys Poulson collect at (801) 355-1234.

WASHINGTON COASTAL COMMUNITY serving a population of 65,000 is actively recruiting the following specialists: Otolaryngologist, Anesthesiologist, Urologist, Pediatrician and Orthopedic Surgeons. A variety of practice support options is available, i.e. office space, relocation assistance, etc. Enjoy the support of major West Coast Catholic Hospital System. Community has close proximity to major recreational areas and easy access to Seattle and Portland. For information send CV and references to: Nancy Friedrich, The Friedrich Group, 9284 Ferncliff N.E., Bainbridge Island, WA 98110.

EUGENE, OREGON: FP/GP to join staff in salaried position with clinic providing outpatient and hospital care primarily to low income population. Half-time to start, flexible scheduling. Contact: Michael Weinstein, MD, 323 East 12th Ave, Eugene, OR 97401; (503) 484-4800.

WASHINGTON: Expanding physician-owned emergency group has opening for full-time career-oriented Emergency Physicians in south central Washington. Excellent benefits including malpractice, disability, health insurance, profit sharing, etc. Flexible work schedules, excellent working and living conditions. Contact Donald Kougl, MD, (307) 632-1436 or send CV to EMP, P.C., PO Box 805, Cheyenne, WY 82003.

FAMILY PRACTITIONER—Out-patient care. Full-time position available for residency trained, Board eligible/Board certified Family Practitioner interested in a position involving out-patient care. Pediatrics, Pre-Natal Care, Adult Medicine, Orthopedics and minor surgery responsibilities are available. For information, call Donald. B. Dawson, Directory of Physician Staffing, toll-free at 1 (800) 446-2255, in California call 1 (800) 336-2255. FHP Professional Staffing, 400 Oceangate Blvd., Suite 1317, Long Beach, CA 90802. For opportunities in Utah, call Maryalys Poulson collect at (801) 355-1234.

INTERNIST or Internal Medicine subspecialist to share medical suite and overhead expenses with recently-established Rheumatologist in excellent Modesto, California, location. Dr Rex Adams, PO Box 5375, Modesto, CA 95352-5375. No phone calls.

GENERAL SURGEON—Surgeon to join an established group of surgeons in Southern California. HMO setting with good support staff and excellent cross coverage for associates. Vascular surgery capabilities are desired. Guaranteed income and benefits. For information, call Donald. B. Dawson, Directory of Physician Staffing, toll-free at 1 (800) 446-2255, in California call 1 (800) 336-2255. FHP Professional Staffing, 400 Oceangate Blvd., Suite 1317, Long Beach, CA 90802. For opportunities in Utah, call Maryalys Poulson collect at (801) 355-1234.

FAMILY PRACTICE opportunity in eastern New Mexico. Join two physicians in private practice situation with an established patient population. Must do OB. No buy-in; just share expenses and call. Family community with stable economy. Contact Bill Norris, Southwest Community Health Services, PO Box 26666, Albuquerque, NM 87125-6666, or call 1 (800) 545-4030, ext. 3050.

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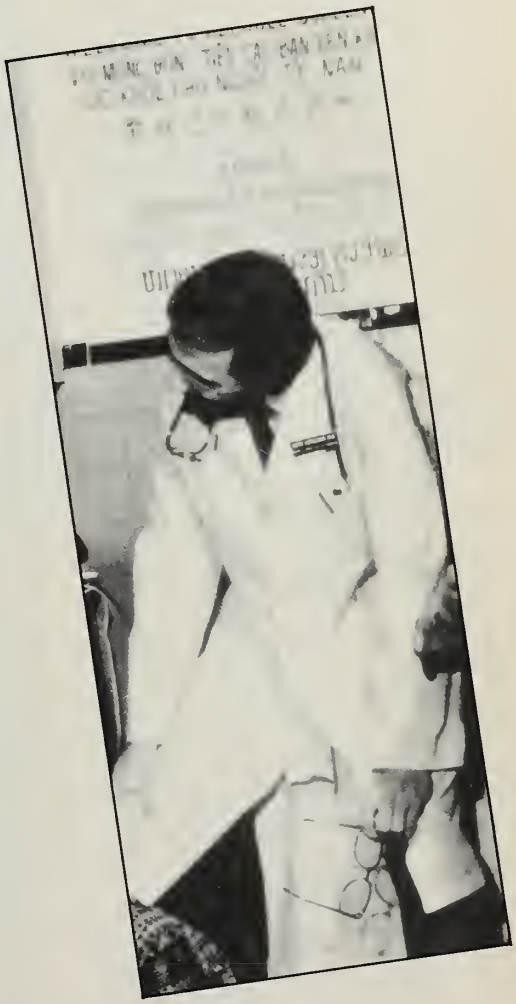

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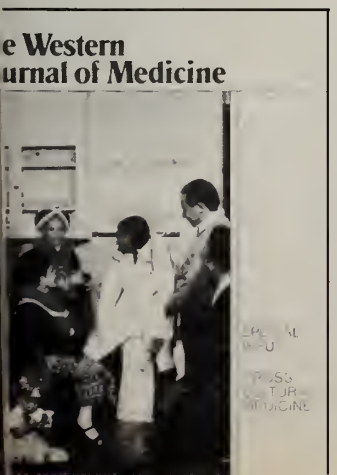

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PHYSICIANS WANTED

INFECTIOUS DISEASE AND INTERNAL MEDICINE—The Division of General Internal Medicine/Primary Care at Cook County Hospital wishes to recruit an Attending Physician to supervise care of both patients with general medical problems and patients with AIDS. Board eligibility in Internal Medicine is required; subspecialty training in Infectious Disease or Oncology is desirable. General Medicine responsibilities occupy 50 percent time and include ward attending and supervising the General Medicine Clinic. AIDS service responsibilities include participation in biweekly clinics and regular ward consultations for patients with AIDS and AIDS related conditions, and involvement in educational and research programs of the AIDS service. Sensitivity to the health care needs of gay men and other AIDS risk group members is needed. Starting salary for Board certified physicians is $54,228/year. For further information please contact Renslow Sherer, MD, Coordinator of AIDS Services, Division of General Medicine, Cook County Hospital, 1835 W. Harrison, Chicago, IL 60612. Cook County Hospital is an Equal Opportunity/Affirmative Action Employer.

GENERAL INTERNIST, downtown Seattle, Washington. Seeking another Internist of FP to join practice emphasizing patient education, psychosocial well-being and the promotion of wellness. Write Julia Smith, 901 Broadway, Seattle, WA 98122 or call (206) 322-0098.

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EXCEPTIONAL OPPORTUNITY—INTERNIST, High quality, aggressive, primary care IM/ID consult/practice in/near Los Angeles suburb looking for the right associate. Only graduates of top medical schools, with excellent university training, willing to work hard need apply. Slight preference for ID training. Send CV to Box 6475, Western Journal of Medicine, 44 Gough St., San Francisco, CA 94103.

WASHINGTON—Ambulatory Care Center, Tacoma. Full- or possibly part-time for FP/IM/EM trained physician. Contact Roger Simms, MD, (206) 759-6655 or reply with CV to 5702 North 26th, Tacoma, WA 98407.

ANESTHESIOLOGIST WANTED. Board certified or eligible. Competitive salary, leading to partnership in small western town. 120 bed hospital. Good schools available, outdoor recreation nearby. Position available June 1. Send CV to: Box 6477, Western Journal of Medicine, 44 Gough St., San Francisco, CA 94103.

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SITUATIONS WANTED

EXPERIENCED Board certified Internist seeks two person association, or small group practice within or close to San Francisco. Spanish spoken. Interested in Occupational Medicine and Disability Evaluations. Please respond to Box 6474, Western Journal of Medicine, 44 Gough St., San Francisco, CA 94103.

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California Medical Association—44 Gough St., San Francisco 94103. (415) 863-5522. Annual Meeting: February 28-March 5, 1986, Bonaventure Hotel, Los Angeles.

Colorado Medical Society—6825 E. Tennessee, Bldg. 2, Suite 500, Denver 80224. (303) 321-8590. Annual Meeting: September 11-14, 1985, Broadmoor, Colorado Springs.

Hawaii Medical Association—320 Ward Ave., Suite 200, Honolulu 96814. (808) 536-7702. Annual Meeting: October 12-14, 1985, Kona Surf Hotel, Kona.

Idaho Medical Association—305 W. Jefferson, PO Box 2668, Boise 83701. (208) 344-7888. Annual Meeting: July 24-27, 1985, Sun Valley.

Montana Medical Association—2012 11th Ave., Suite 12, Helena 59601. (406) 443-4000. Annual Meeting: October 3-5, 1985, Outlaw Inn, Kalispell.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: 1986: date and place to be announced.

New Mexico Medical Society—303 San Mateo NE, Suite 204, Albuquerque 87108. (505) 266-7868. Annual Meeting: 1986: date and place to be announced.

Oregon Medical Association—5210 S.W. Corbett Ave., Portland 97201. (503) 226-1555. Annual Meeting: (House of Delegates only): 1986: date and place to be announced.

Utah State Medical Association—540 East Fifth South, Salt Lake City 84102. (801) 355-7477. Annual Meeting: September 26-27, 1985. Hotel Utah, Salt Lake City.

Washington State Medical Association—900 United Airlines Bldg., 2033 6th Ave., Seattle 98121. (206) 623-4801. Annual Meeting: September 19-22, 1985, Jantzen Beach.

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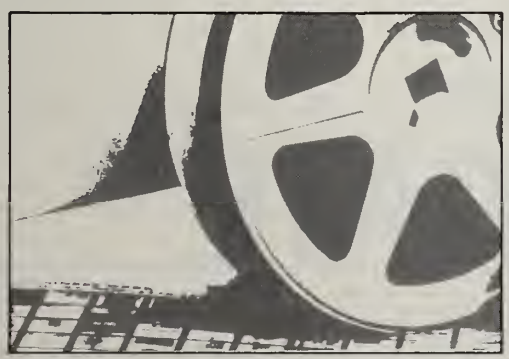

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SORBITRATE®
(ISOSORBIDE DINITRATE)

Please consult full prescribing information before use. A summary follows:

INDICATIONS AND USAGE: SORBITRATE (isosorbide dinitrate) is indicated for the treatment and prevention of angina pectoris. All dosage forms of isosorbide dinitrate may be used prophylactically to decrease frequency and severity of anginal attacks and can be expected to decrease the need for sublingual nitroglycerin.

The sublingual and chewable forms of the drug are indicated for acute prophylaxis of angina pectoris when taken a few minutes before situations likely to provoke anginal attacks. Because of a slower onset of effect, the oral forms of isosorbide dinitrate are not indicated for acute prophylaxis.

CONTRAINDICATIONS: SORBITRATE is contraindicated in patients who have shown purported hypersensitivity or idiosyncrasy to it or other nitrates or nitrites. Epinephrine and related compounds are ineffective in reversing the severe hypotensive events associated with overdose and are contraindicated in this situation.

WARNINGS: The benefits of SORBITRATE during the early days of an acute myocardial infarction have not been established. If one elects to use organic nitrates in early infarction, hemodynamic monitoring and frequent clinical assessment should be used because of the potential deleterious effects of hypotension.

PRECAUTIONS: General: Severe hypotensive response, particularly with upright posture, may occur with even small doses of SORBITRATE. The drug should therefore be used with caution in subjects who may have blood volume depletion from diuretic therapy or in subjects who have low systolic blood pressure (eg, below 90 mmHg). Paradoxical bradycardia and increased angina pectoris may accompany nitrate-induced hypotension. Nitrate therapy may aggravate the angina caused by hypertrophic cardiomyopathy.

Marked symptomatic, orthostatic hypotension has been reported when calcium channel blockers and organic nitrates were used in combination. Dose adjustment of either class of agents may be necessary.

Tolerance to this drug and cross-tolerance to other nitrates and nitrites may occur. Tolerance to the vascular and antianginal effects of isosorbide dinitrate or nitroglycerin has been demonstrated in clinical trials, experience through occupational exposure, and in isolated tissue experiments in the laboratory. The importance of tolerance to the appropriate use of isosorbide dinitrate in the management of patients with angina pectoris has not been determined. However, one clinical trial using treadmill exercise tolerance (as an end point) found an 8-hour duration of action of oral isosorbide dinitrate following the first dose (after a 2-week placebo washout) and only a 2-hour duration of effect of the same dose after 1 week of repetitive dosing at conventional dosing intervals. On the other hand, several trials have been able to differentiate isosorbide dinitrate from placebo after 4 weeks of therapy and, in open trials, an effect seems detectable for as long as several months.

Tolerance clearly occurs in industrial workers continuously exposed to nitroglycerin. Moreover, physical dependence also occurs since chest pain, acute myocardial infarction, and even sudden death have occurred during temporary withdrawal of nitroglycerin from the workers. In clinical trials in angina patients, there are reports of anginal attacks being more easily provoked and of rebound in the hemodynamic effects soon after nitrate withdrawal. The relative importance of these observations to the routine, clinical use of isosorbide dinitrate is not known. However, it seems prudent to gradually withdraw patients from isosorbide dinitrate when the therapy is being terminated, rather than stopping the drug abruptly.

Information for Patients: Headache may occur during initial therapy with SORBITRATE. Headache is usually relieved by the use of standard headache remedies or by lowering the dose and tends to disappear after the first week or two of use.

Drug Interactions: Alcohol may enhance any marked sensitivity to the hypotensive effect of nitrates.

Isosorbide dinitrate acts directly on vascular smooth muscle; therefore, any other agent that depends on vascular smooth muscle as the final common path can be expected to have decreased or increased effect depending on the agent.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No long-term studies in animals have been performed to evaluate the carcinogenic potential of this drug. A modified two-litter reproduction study in rats fed isosorbide dinitrate at 25 or 100 mg/kg/day did not reveal any effects on fertility or gestation or any remarkable gross pathology in any parent or offspring fed isosorbide dinitrate as compared with rats fed a basal-controlled diet.

Pregnancy Category C: Isosorbide dinitrate has been shown to cause a dose-related increase in embryotoxicity (increase in mummified pups) in rabbits at oral doses 35 and 150 times the maximum recommended human daily dose. There are no adequate and well-controlled studies in pregnant women. SORBITRATE should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when SORBITRATE is administered to a nursing woman.

Pediatric Use: The safety and effectiveness of SORBITRATE in children has not been established.

ADVERSE REACTIONS: Adverse reactions, particularly headache and hypotension, are dose-related. In clinical trials at various doses, the following have been observed.

Headache is the most common (reported incidence varies widely, apparently being dose-related, with an average occurrence of about 25%) adverse reaction and may be severe and persistent. Cutaneous vasodilation with flushing may occur. Transient episodes of dizziness and weakness, as well as other signs of cerebral ischemia associated with postural hypotension, may occasionally develop (the incidence of reported symptomatic hypotension ranges from 2% to 36%). An occasional individual will exhibit marked sensitivity to the hypotensive effects of nitrates and severe responses (nausea, vomiting, weakness, restlessness, pallor, perspiration, and collapse) may occur even with the usual therapeutic dose. Drug rash and/or exfoliative dermatitis may occasionally occur. Nausea and vomiting appear to be uncommon. Case reports of clinically significant methemoglobinemia are rare at conventional doses of organic nitrates. The formation of methemoglobin is dose-related and, in the case of genetic abnormalities of hemoglobin that favor methemoglobin formation, even conventional doses of organic nitrate could produce harmful concentrations of methemoglobin.

DOSAGE AND ADMINISTRATION: For the treatment of angina pectoris, the usual starting dose for sublingual SORBITRATE is 2.5 to 5 mg, for chewable tablets, 5 mg, for oral (swallowed) tablets, 5 to 20 mg, and for controlled-release forms, 40 mg.

SORBITRATE should be titrated upward until angina is relieved or side effects limit the dose. In ambulatory patients, the magnitude of the incremental dose increase should be guided by measurements of standing blood pressure.

The initial dosage of sublingual or chewable SORBITRATE for prophylactic therapy in angina pectoris patients is generally 5 or 10 mg every 2 to 3 hours. Adequate controlled clinical studies demonstrating the effectiveness of chronic maintenance therapy with these dosage forms have not been reported.

SORBITRATE in oral doses of 10 to 40 mg given every 6 hours or in oral controlled-release doses of 40 to 80 mg given every 8 to 12 hours is generally recommended. The extent to which development of tolerance should modify the dosage program has not been defined. *The oral controlled-release forms of isosorbide dinitrate should not be chewed.*

DOSAGE FORMS AVAILABLE: Sublingual Tablets (2.5, 5, 10 mg), Chewable Tablets (5, 10 mg), Oral Tablets (5, 10, 20, 30, 40 mg), Sustained Action Tablets (40 mg).

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See following page.

CAPOTEN® (captopril tablets) is almost never associated with fatigue (unlike beta-blockers and CNS active agents: e.g., clonidine, methyldopa).[‡1]

CAPOTEN is almost never associated with loss of libido and impotence (unlike beta-blockers and CNS active agents).[‡1,2]

[†]CAPOTEN is indicated for the treatment of hypertensive patients who on multidrug regimens either have failed to respond satisfactorily or have developed unacceptable side effects.

Please see the WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS sections of the brief summary on adjacent pages.

SQUIBB

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CAPOTEN® BID
captopril tablets

HYPERTENSION CONTROL† PATIENTS CAN FEEL GOOD ABOUT

CAPOTEN is almost never associated with mental impairment (unlike beta-blockers and CNS active agents).‡[3]

ACE*INHIBITOR
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captopril tablets

HELP PUT QUALITY BACK INTO LIVING

*Angiotensin Converting Enzyme

†The most frequently occurring adverse reactions associated with CAPOTEN are skin rash and taste alteration; both effects are generally mild, reversible, or self-limited.

ACE INHIBITOR

CAPOTEN® BID
captopril tablets

Precautionary guidelines

CAPOTEN® (captopril tablets) has been associated with the development of neutropenia/agranulocytosis (0.3% of 4,000 patients) or proteinuria (1.2% of 4,000 patients).† These serious side effects are more likely to occur in patients with predisposing conditions, such as renal impairment or autoimmune disease, or in patients receiving therapy known to suppress the immune response. The following precautionary guidelines are recommended for all patients receiving CAPOTEN:

☐ Obtain urinary protein level estimates prior to initiating therapy, at monthly intervals for the first nine months of treatment, and periodically thereafter.

☐ Obtain WBC counts at the initiation of therapy, at two-week intervals for the first three months of treatment, and periodically thereafter.

☐ Carefully review the WARNINGS and ADVERSE REACTIONS sections in the complete prescribing information, with particular attention to the patient at increased risk.

☐ The most frequently occurring adverse reactions are skin rash and taste alteration; both effects are generally mild, reversible, or self-limited.

References

1. The 1984 Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure. US Department of Health and Human Services. June 1984
2. Stevenson JG, Umstead GS. Sexual dysfunction due to antihypertensive agents. Drug Intell Clin Pharm 18:113-121, 1984
3. Solomon S, Hotchkiss E, Saravay SM, et al: Impairment of memory function by antihypertensive medication. Arch Gen Psychiatry 40:1109-1112, 1983.

*Angiotensin Converting Enzyme

†Please see brief summary for INDICATIONS AND USAGE, WARNINGS, and ADVERSE REACTIONS.

CAPOTEN® TABLETS
Captopril Tablets

INDICATIONS: Hypertension – Because serious adverse effects have been reported (see WARNINGS), CAPOTEN is indicated for treatment of hypertensive patients who on multidrug regimens have either failed to respond satisfactorily or developed unacceptable side effects.

Heart Failure: CAPOTEN (captopril) is indicated in patients with heart failure who have not responded adequately to or cannot be controlled by conventional diuretic and digitalis therapy. CAPOTEN is to be used with diuretics and digitalis.

WARNINGS: Proteinuria – Total urinary proteins >1 g/day were seen in 1.2% of patients on captopril; the nephrotic syndrome occurred in about one-fourth of these cases. About 60% of affected patients had evidence of prior renal disease; the remainder had no known renal dysfunction. In most cases, proteinuria subsided or cleared within 6 months whether or not captopril was continued. The BUN and creatinine were seldom altered in proteinuric patients.

Membranous glomerulopathy was found in nearly all of the proteinuric patients on captopril who were biopsied and may be drug related. Most cases of proteinuria occurred by the eighth month of therapy. Patients should have urinary protein estimates (dip-stick on first morning urine, or quantitative 24-hour urine – the latter provides greater precision when proteinuria is persistent and/or at low levels) before therapy, at approximate monthly intervals for the first nine months of therapy, and periodically thereafter. For patients who develop proteinuria >1 g/day, or increasing proteinuria, the benefits and risks of continuing captopril should be evaluated.

Neutropenia/Agranulocytosis – Neutropenia (<300/mm³) associated with myeloid hypoplasia (probably drug related) occurred in about 0.3% of captopril treated patients. About half of the neutropenic patients developed systemic or oral cavity infections or other features of agranulocytosis. Most of the neutropenic patients had severe hypertension and renal function impairment; about half had systemic lupus erythematosus (SLE), or another autoimmune/collagen disorder; multiple concomitant drug therapy was common, including immunosuppressive therapy in a few cases. Daily doses of captopril in the leukopenic patients were relatively high, particularly in view of their diminished renal function. The neutropenia appeared 3 to 12 weeks after starting captopril; it developed relatively slowly, taking 10 to 30 days to have white blood count fall to its nadir; neutrophils returned to normal in about two weeks (other than two patients who died of sepsis).

Use captopril with caution in patients with impaired renal function, serious autoimmune disease (particularly SLE), or who are exposed to other drugs known to affect the white cells or immune response. In patients at particular risk (as noted above), perform white blood cell and differential counts prior to therapy, at about 2-week intervals for about the first 3 months of therapy, and periodically thereafter.

The risk of neutropenia in patients who are less seriously ill or who receive lower dosages appears to be smaller. In these patients white blood cell counts should be performed every 2 weeks for the first 3 months of therapy, and periodically thereafter. Perform differential counts when leukocytes are <4000/mm³ or the pretherapy white count is halved. All patients treated with captopril should be told to report any signs of infection (e.g., sore throat; fever); if infection is suspected, perform counts without delay. Since discontinuation of captopril and other drugs has generally led to prompt return of the white count to normal, upon confirmation of neutropenia (neutrophil count <1000/mm³) withdraw captopril and closely follow the patient's course.

Hypotension – Excessive hypotension was rarely seen in hypertensive patients but is a possibility in severely salt/volume-depleted persons such as those treated vigorously with diuretics (see PRECAUTIONS [Drug Interactions]).

In heart failure, where blood pressure was either normal or low, transient decreases in mean blood pressure >20% were recorded in about half of the patients. This transient hypotension may occur after any of the first several doses and is usually well tolerated, although rarely it has been associated with arrhythmia or conduction defects. A starting dose of 6.25 or 12.5 mg tid may minimize the hypotensive effect. Patients should be followed closely for the first two weeks of treatment and whenever the dose of captopril and/or diuretic is increased.

BECAUSE OF THE POTENTIAL FALL IN BLOOD PRESSURE IN THESE PATIENTS, THERAPY SHOULD BE STARTED UNDER VERY CLOSE MEDICAL SUPERVISION.

PRECAUTIONS: General: *Impaired Renal Function,* Hypertension – Some hypertensive patients with renal disease, particularly those with severe renal artery stenosis, have developed increases in BUN and serum creatinine. It may be necessary to reduce captopril dosage and/or discontinue diuretic. For some of these patients, normalization of blood pressure and maintenance of adequate renal perfusion may not be possible. Heart Failure – About 20% of patients develop stable elevations of BUN and serum creatinine >20% above normal or baseline upon long-term treatment. Less than 5% of patients, generally with severe preexisting renal disease, required discontinuation due to progressively increasing creatinine. See DOSAGE AND ADMINISTRATION, ADVERSE REACTIONS [Altered Laboratory Findings]. *Valvular Stenosis* – A theoretical concern, for risk of decreased coronary perfusion, has been noted regarding vasodilator treatment in patients with aortic stenosis, due to decreased afterload reduction.

Surgery/Anesthesia – If hypotension occurs during major surgery or anesthesia, and is considered due to the effects of captopril, it is correctable by volume expansion.

Drug Interactions: *Hypotension: Patients on Diuretic Therapy* – Precipitous reduction of blood pressure may occasionally occur within the first 3 hours after administration of the initial captopril dose in patients on diuretics, especially those recently placed on diuretics and those on severe dietary salt restriction or dialysis. This possibility can be minimized by either discontinuing the diuretic or increasing the salt intake about 1 week prior to initiation of captopril therapy. Alternatively, provide medical supervision for at least 3 hours after the initial dose in hypertensive patients.

Agents Having Vasodilator Activity – In heart failure patients vasodilators should be administered with caution.

Agents Causing Renin Release – Captopril's effect will be augmented by antihypertensive agents that cause renin release.

Agents Affecting Sympathetic Activity – The sympathetic nervous system may be especially important in supporting blood pressure in patients receiving captopril alone or with diuretics. Beta-adrenergic blocking drugs add some further antihypertensive effect to captopril, but the overall response is less than additive. Therefore, use agents affecting sympathetic activity (e.g., ganglionic blocking agents or adrenergic neuron blocking agents) with caution.

Agents Increasing Serum Potassium – Give potassium-sparing diuretics or potassium supplements only for documented hypokalemia, and then with caution, since they may lead to a significant increase of serum potassium.

Drug/Laboratory Test Interaction: Captopril may cause a false-positive urine test for acetone.

Carcinogenesis, Mutagenesis and Impairment of Fertility: Two-year studies with doses of 50 to 1350 mg/kg/day in mice and rats failed to show any evidence of carcinogenic potential. Studies in rats have revealed no impairment of fertility.

Usage in Pregnancy: There are no adequate and well-controlled studies in pregnant women. Embryocidal effects were observed in rabbits. Therefore, captopril should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.

(continued on next page)

SQUIBB®

INNOVATORS IN CARDIOVASCULAR MEDICINE

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Nursing Mothers: Captopril is secreted in human milk. Exercise caution when administering captopril to a nursing woman, and, in general, nursing should be interrupted.

Pediatric Use: Safety and effectiveness in children have not been established although there is limited experience with use of captopril in children from 2 months to 15 years of age. Dosage, on a weight basis, was comparable to that used in adults. Captopril should be used in children only if other measures for controlling blood pressure have not been effective.

ADVERSE REACTIONS: Reported incidences are based on clinical trials involving approximately 4000 patients.

Renal—One to 2 of 100 patients developed proteinuria (see WARNINGS). Renal insufficiency, renal failure, polyuria, oliguria, and urinary frequency in 1 to 2 of 1000 patients.

Hematologic—Neutropenia/agranulocytosis occurred in about 0.3% of captopril-treated patients (see WARNINGS). Two of these patients developed sepsis and died.

Dermatologic—Rash (usually maculopapular, rarely urticarial), often with pruritus and sometimes with fever and eosinophilia, in about 10 of 100 patients, usually during the first 4 weeks of therapy. Pruritus, without rash, in about 2 of 100 patients. A reversible associated pemphigoid-like lesion, and photosensitivity have also been reported. Angioedema of the face, mucous membranes of the mouth, or of the extremities in about 1 of 100 patients—reversible on discontinuance of captopril therapy. One case of laryngeal edema reported. Flushing or pallor in 2 to 5 of 1000 patients.

Cardiovascular—Hypotension in about 2 of 100 patients. See WARNINGS (Hypotension) and PRECAUTIONS (Drug Interactions) for discussion of hypotension on initiation of captopril therapy. Tachycardia, chest pain, and palpitations each in about 1 of 100 patients. Angina pectoris, myocardial infarction, Raynaud's syndrome, and congestive heart failure each in 2 to 3 of 1000 patients.

Dysgeusia—About 7 of 100 patients developed a diminution or loss of taste perception; taste impairment is reversible and usually self-limited even with continued drug use (2 to 3 months). Gastric irritation, abdominal pain, nausea, vomiting, diarrhea, anorexia, constipation, aphthous ulcers, peptic ulcer, dizziness, headache, malaise, fatigue, insomnia, dry mouth, dyspnea, and paresthesias reported in about 0.5 to 2% of patients but did not appear at increased frequency compared to placebo or other treatments used in controlled trials.

Altered Laboratory Findings: Elevations of liver enzymes in a few patients although no causal relationship has been established. Rarely cholestatic jaundice and hepatocellular injury with secondary cholestasis, have been reported. A transient elevation of BUN and serum creatinine may occur, especially in volume-depleted or renovascular hypertensive patients. In instances of rapid reduction of longstanding or severely elevated blood pressure, the glomerular filtration rate may decrease transiently, also resulting in transient rises in serum creatinine and BUN. Small increases in serum potassium concentration frequently occur, especially in patients with renal impairment (see PRECAUTIONS).

OVERDOSAGE: Primary concern in correction of hypotension. Volume expansion with an I.V. infusion of normal saline is the treatment of choice for restoration of blood pressure. Captopril may be removed from the general circulation by hemodialysis.

DOSAGE AND ADMINISTRATION: CAPOTEN (captopril) should be taken one hour before meals. In hypertension, CAPOTEN may be dosed bid or tid. Dosage must be individualized; see DOSAGE AND ADMINISTRATION section of package insert for detailed information regarding dosage in hypertension and in heart failure. Because CAPOTEN (captopril) is excreted primarily by the kidneys, dosage adjustments are recommended for patients with impaired renal function.

Consult package insert before prescribing CAPOTEN (captopril).

HOW SUPPLIED: Available in tablets of 12.5, 25, 50, and 100 mg in bottles of 100 (25 mg also available in bottles of 1000), and in UNIMATIC® single dose packs of 100 tablets. (J3-658B)

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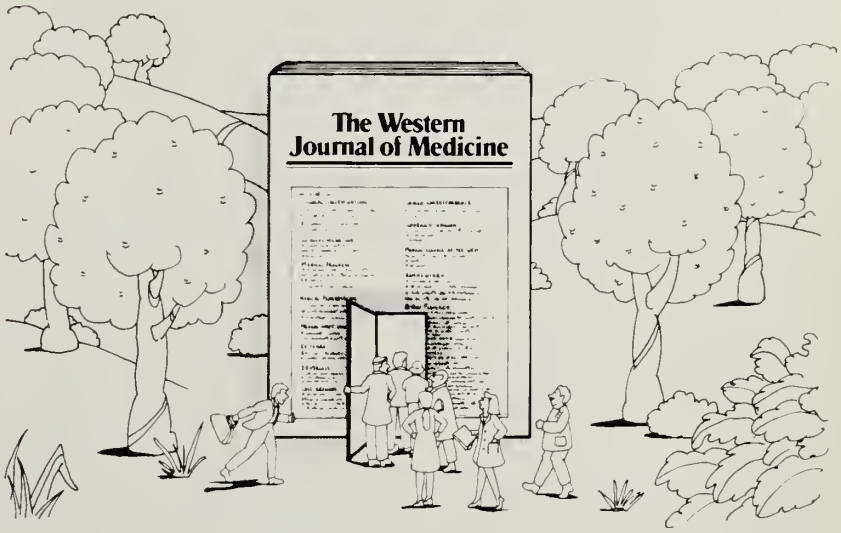

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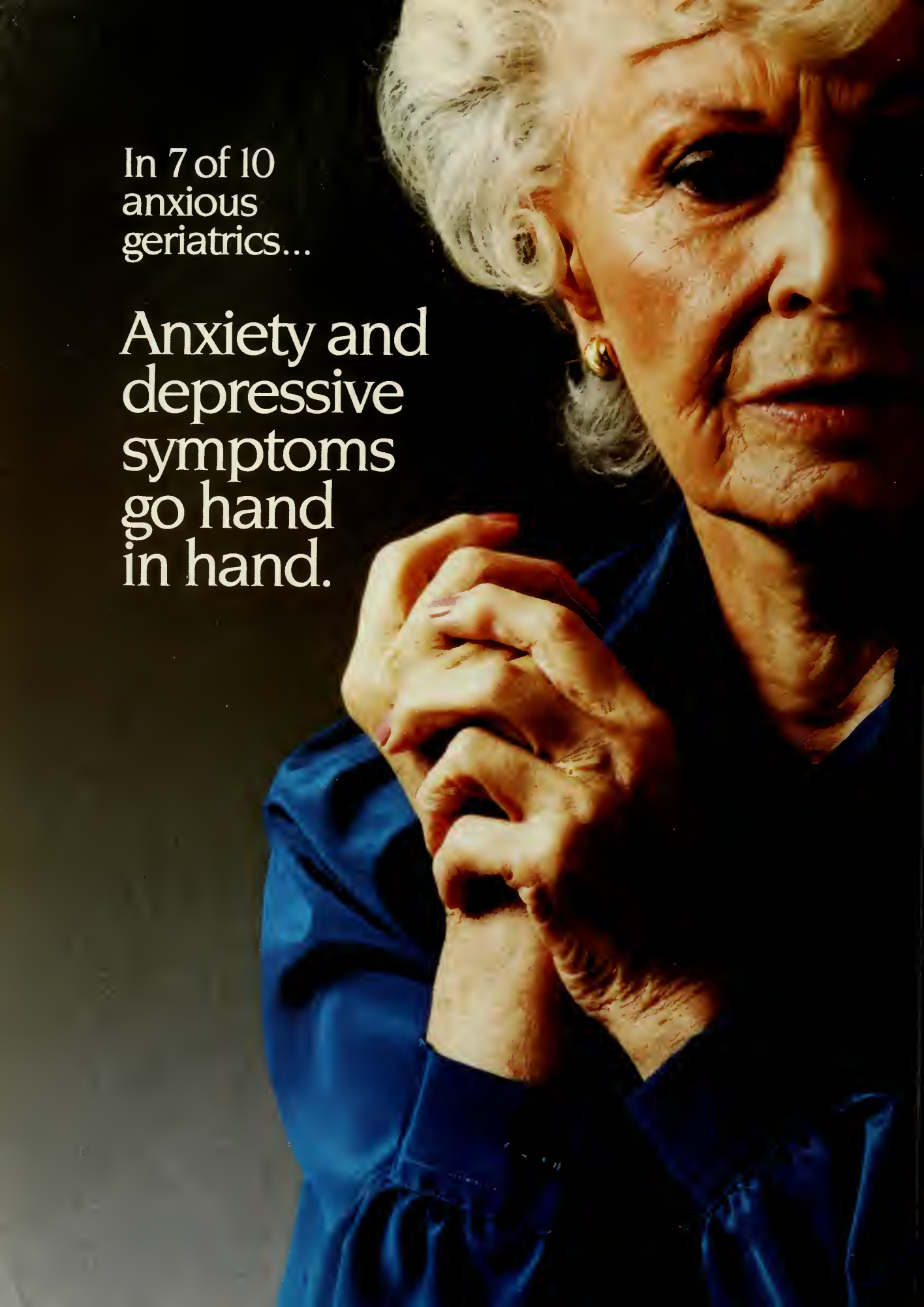
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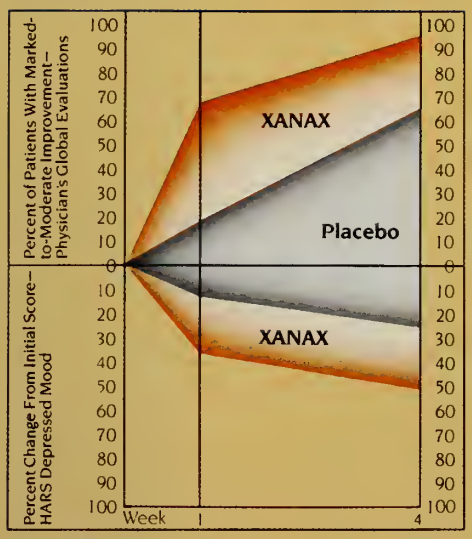
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XANAX
Placebo
Percent Change From Initial Score—HARS Depressed Mood
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XANAX
Week 1 4

In a recent clinical study[1] of 83 geriatric patients with clinical anxiety, 73% were diagnosed as having symptoms of depressed mood.

XANAX is well suited for therapy because it demonstrates greater efficacy than placebo in reducing the Hamilton Anxiety Rating Scale Total Score and individual items including depressed mood (see Figure).

With clinical advantages for geriatric patients.

- **Rapidly relieves** the symptoms of anxiety
- **Rapidly relieves** associated depressed mood
- **Well tolerated**—mild, transient drowsiness, the most commonly reported side effect the first week of therapy, shows a marked decrease thereafter and is not significantly different from that of placebo
- **Does not cause** cardiotoxicity
- **Specific geriatric dosage**—0.25 mg, two or three times daily

1. Cohn JB: Double-blind safety and efficacy comparison of alprazolam and placebo in the treatment of anxiety in geriatric patients. *Curr Ther Res* 1984;35(1):100-112

Xanax® 0.25 mg Tablets
alprazolam C IV

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Upjohn THE UPJOHN COMPANY
Kalamazoo, Michigan 49001 USA

Please see next page for brief summary of prescribing information.

XANAX® Tablets
(alprazolam) ℞

CONTRAINDICATIONS
Patients with sensitivity to this drug or other benzodiazepines and in acute narrow angle glaucoma

WARNINGS
Not of value in psychotic patients Caution patients against hazardous occupations requiring complete mental alertness and about the simultaneous ingestion of alcohol and other CNS depressant drugs

Benzodiazepines can cause fetal harm in pregnant women. Warn patients of the potential hazard to the fetus. Avoid during the first trimester.

PRECAUTIONS
General: The dosage of XANAX Tablets should be reduced or withdrawn gradually, since withdrawal seizures have been reported upon abrupt withdrawal. If XANAX is combined with other psychotropics or anticonvulsant drugs, consider drug potentiation. (See Drug Interaction section.) Exercise the usual precautions regarding size of the prescription for depressed or suicidal patients. In elderly and debilitated patients, use the lowest possible dosage. (See Dosage and Administration.) Observe the usual precautions in treating patients with impaired renal or hepatic function.

Information for Patients: Alert patients about, (a) consumption of alcohol and drugs, (b) possible fetal abnormalities, (c) operating machinery or driving, (d) not increasing dose of the drug due to risk of dependence, (e) not stopping the drug abruptly *Laboratory Tests:* Not ordinarily required in otherwise healthy patients. *Drug Interactions:* Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistamines, ethanol and other CNS depressants. Pharmacokinetic interactions with benzodiazepines have been reported *Drug/Laboratory Test Interactions:* No consistent pattern for a specific drug or specific test. *Carcinogenesis, Mutagenesis, Impairment of Fertility* No carcinogenic potential or impairment of fertility in rats. *Pregnancy* See Warnings. *Nonteratogenic Effects:* The child born of a mother on benzodiazepines may be at some risk for withdrawal symptoms and neonatal flaccidity *Labor and Delivery* No established use. *Nursing Mothers:* Benzodiazepines are excreted in human milk. Women on XANAX should not nurse *Pediatric Use:* Safety and effectiveness in children below the age of 18 have not been established

ADVERSE REACTIONS
Side effects are generally observed at the beginning of therapy and usually disappear with continued medication. In the usual patient, the most frequent side effects are likely to be an extension of the pharmacological activity of XANAX, e.g., drowsiness or lightheadedness.

Central nervous system Drowsiness, lightheadedness, depression, headache, confusion, insomnia, nervousness, syncope, dizziness, akathisia, and tiredness/sleepiness

Gastrointestinal: Dry mouth, constipation, diarrhea, nausea/vomiting, and increased salivation.

Cardiovascular: Tachycardia/palpitations, and hypotension.

Sensory Blurred vision.

Musculoskeletal: Rigidity and tremor.

Cutaneous: Dermatitis/allergy

Other side effects: Nasal congestion, weight gain, and weight loss.

In addition, the following adverse events have been reported with the use of anxiolytic benzodiazepines: dystonia, irritability, concentration difficulties, anorexia, loss of coordination, fatigue, sedation, slurred speech, jaundice, musculoskeletal weakness, pruritus, diplopia, dysarthria, changes in libido, menstrual irregularities, incontinence and urinary retention.

Paradoxical reactions such as stimulation, agitation, increased muscle spasticity, sleep disturbances, and hallucinations may occur. Should these occur, discontinue the drug.

During prolonged treatment, periodic blood counts, urinalysis, and blood chemistry analysis are advisable. Minor EEG changes, of unknown significance, have been observed

DRUG ABUSE AND DEPENDENCE
Physical and Psychological Dependence: Withdrawal symptoms have occurred following abrupt discontinuance of benzodiazepines. Withdrawal seizures have occurred upon rapid decrease or abrupt discontinuation of therapy. In all patients, dosage should be gradually tapered under close supervision. Patients with a history of seizures or epilepsy should not be abruptly withdrawn from XANAX. Addiction-prone individuals should be under careful surveillance. *Controlled Substance Class:* XANAX is a controlled substance and has been assigned to schedule IV.

DOSAGE AND ADMINISTRATION
The usual starting dose is 0.25 to 0.5 mg, t.i.d. Maximum total daily dose is 4 mg. In the elderly or debilitated, the usual starting dose is 0.25 mg, two or three times daily Reduce dosage gradually when terminating therapy, by no more than one milligram every three days.

CAUTION FEDERAL LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION. B-3-S

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Books Received

Books received by THE WESTERN JOURNAL OF MEDICINE *are acknowledged in this column. Selections will be made for more extensive review in the interest of readers as space permits.*

GASTROINTESTINAL SURGERY—2 Volumes—Edited by David Fromm, MD, Professor and Chairman, Department of Surgery, State University of New York, Upstate Medical Center, Syracuse, New York. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1984 933 pages, $135.

GENITOURINARY CANCER—Volume 5 in CONTEMPORARY ISSUES IN CLINICAL ONCOLOGY—Edited by Marc B. Garnick, MD, Associate Professor of Medicine, Harvard Medical School, Dana-Farber Cancer Institute, and Associate Physician, Brigham and Women's Hospital, Boston. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1984. 272 pages, $39.50.

LEUKEMIAS AND LYMPHOMAS—Edited by Peter H. Wiernik, MD, Gutman Professor and Chairman, Department of Oncology, Montefiore Medical Center; Chief, Division of Medical Oncology, Albert Einstein College of Medicine, and Associate Director for Clinical Research, Albert Einstein Cancer Center, New York. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1984. 271 pages, $36.

LIPOPLASTY—The Theory and Practice of Blunt Suction Lipectomy—Edited by Gregory P. Hetter, MD, Assistant Clinical Professor of Plastic Surgery, University of Nevada School of Medicine, Reno; Assistant Chief, Division of Plastic Surgery, Sunrise Hospital, Las Vegas; Foreword by Mario Gonzalez Ulloa, MD, Director, Dalinde Medical Center, Mexico City. Little, Brown and Company, Medical Division, 34 Beacon St, Boston, MA 02106, 1984. 340 pages, $95.

MANUAL OF OBSTETRIC ANESTHESIA—Edited by Gerard W. Ostheimer, MD, Associate Professor of Anesthesia, Harvard Medical School, and Director of Obstetric Anesthesia, Brigham and Women's Hospital, Boston. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1984. 412 pages, $27.50 (paperback).

MECHANICAL VENTILATION—Edited by Robert R. Kirby, MD, Col USAF, MC, Chairman, Department of Anesthesiology, Wilford Hall USAF Medical Center, Lackland Air Force Base, Texas, and Clinical Professor of Anesthesiology, University of Texas Health Sciences Center, San Antonio, and Tulane University School of Medicine, New Orleans; Robert A. Smith, MS, RRT, Technical Director, Critical Care Medicine Research and Training Laboratory, Memorial Medical Center, Jacksonville, Florida, and David A. Desautels, MPA, RRT, Director, Hyperbaric Medicine Program, Hospital Information System Liaison to Operations, Shands Hospital at the University of Florida, Gainesville. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1984. 474 pages, $45.

NEUROMUSCULAR MANIFESTATIONS OF SYSTEMIC DISEASE—Robert B. Layzer, MD, Professor of Neurology, University of California, San Francisco, School of Medicine. F. A. Davis Co, 1915 Arch St, Philadelphia, PA 19103, 1984. 409 pages, $60.

OCCUPATION PROTECTION AND HEALTH PROMOTION—Special Edition of *Health Education Quarterly* (Publication of the Society for Health Education)—Vol 11—Editor: David A. Sleet. John Wiley & Sons, Inc, Journals Division, 605 Third Ave, New York, NY 10158, 1984. 110 pages, $10.

OCCUPATIONAL LOW BACK PAIN—Edited by Malcolm H. Pope, PhD, Professor of Orthopaedics and Professor of Mechanical Engineering; John W. Frymoyer, MD, Professor of Orthopaedics and Rehabilitation, University of Vermont, Burlington, and Gunnar B. J. Andersson, MD, Associate Professor of Orthopaedic Surgery, University of Göteborg, Sweden. Praeger, 521 Fifth Ave, New York, NY 10175, 1984. 344 pages, $41.95.

PATHOLOGY OF THE ESOPHAGUS, STOMACH, AND DUODENUM—Edited by Henry D. Appelman, MD, Professor of Pathology and Director, Anatomic Pathology, University of Michigan Medical School, Ann Arbor. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1984. 284 pages, $49.50.

PEDIATRIC NEUROLOGIC PHYSICAL THERAPY—Edited by Suzann K. Campbell, PhD, LPT, Professor, Division of Physical Therapy, Department of Medical Allied Health Professions, School of Medicine, University of North Carolina at Chapel Hill. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1984. 413 pages, $29.

PERSONAL PENSION PLAN STRATEGIES FOR PHYSICIANS—C. Colburn Hardy and Howard J. Weiner, JD, LLM. Medical Economics Books, Box C-779, Pratt Station, Brooklyn, NY 11205, 1985. 132 pages, $19.95* (plus $2 handling). *Prices are subject to change without notice.

PRACTICAL MANAGEMENT OF STROKE—Graham P. Mulley, DM, MRCP, Consultant Geriatrician, Department of Medicine for the Elderly, St James University Hospital, Leeds, England. Medical Economics Books, Oradell, NJ 07649, 1985. 167 pages, $18.95.

PULMONARY FUNCTION TESTING—PRINCIPLES AND PRACTICE—Edited by Steven A. Conrad, MD, Instructor, Department of Medicine, and Clinical Assistant Professor, Department of Physiology and Biophysics; Gary T. Kinasewitz, MD, Associate Professor, Pulmonary Diseases Section, Department of Medicine, and Department of Physiology and Biophysics, and Ronald B. George, MD, Professor and Chief, Pulmonary Diseases Section, Department of Medicine, and Medical Director, Department of Respiratory Therapy, Louisiana State University Medical Center, Shreveport. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1984. 365 pages, $33.50.

RADIONUCLIDE SCINTIGRAPHY IN ORTHOPAEDICS—Edited by C. S. B. Galasko, MB, BCh, MSc, ChM, FRCS(Eng), FRCS(Ed), Professor of Orthopaedic Surgery, University of Manchester, England, and David A. Weber, PhD, Associate Professor of Radiology, University of Rochester, Rochester, New York. Churchill Livingstone Inc, 1560 Broadway, New York, NY 10036, 1984. 260 pages, $55.

SKIN PROBLEMS OF THE AMPUTEE—S. William Levy, MD, Research Associate, Biomechanics Laboratory, and Clinical Professor of Dermatology, University of California, San Francisco. Warren H. Green, Inc, 8356 Olive Blvd, St Louis, MO 63132, 1983. 304 pages, $39.95.

SURGICAL TREATMENT OF THE INFERTILE FEMALE—Veasy C. Buttram, Jr, MD, Professor and Director, Division of Endocrinology-Fertility, Department of Obstetrics and Gynecology, Baylor College of Medicine, Houston, and Robert C. Reiter, MD, Resident, Obstetrics and Gynecology, Naval Regional Medical Center, San Diego. Williams & Wilkins, 428 East Preston Street, Baltimore, MD 21202, 1985. 370 pages; price not given.

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ZORprin® is not recommended for children under 12 years of age; it is contraindicated in all children with fever accompanied by dehydration. ▫ **WARNINGS**: ZORprin® should be used with caution when anticoagulants are prescribed concurrently, since aspirin may depress the concentration of prothrombin in plasma and increase bleeding time. Large doses of salicylates may have hypoglycemic action and enhance the effect of the oral hypoglycemics; concomitant use therefore is not recommended. However, if such use is necessary, dosage of the hypoglycemic agent must be reduced. The hypoglycemic action of the salicylates may also necessitate adjustment of the insulin requirements of diabetics. While salicylates in large doses have a uricosuric effect, smaller amounts may reduce the uricosuric effect of uricosuric agents. ▫ **USE IN PREGNANCY**: Aspirin can cause fetal harm when administered to pregnant women. Aspirin interferes with maternal and infant blood clotting and may lengthen the duration of pregnancy and parturition. Aspirin has produced teratogenic effects and increases the incidence of stillbirths and neonatal deaths in animals. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Aspirin should not be taken during the last 3 months of pregnancy. ▫ **PRECAUTIONS**: Appropriate precautions should be taken in prescribing ZORprin® for patients who are known to be sensitive to aspirin or salicylates. Particular care should be used when prescribing this medication for patients with erosive gastritis, peptic ulcer, mild diabetes or gout. As with all salicylate drugs, caution should be exercised in prescribing ZORprin® for those patients with bleeding tendencies or those on anticoagulant drugs. Large doses of salicylates should be avoided in patients with clear evidence of carditis. In order to avoid exacerbation of disease or adrenal insufficiency, patients who have been on prolonged corticosteroid therapy should have their therapy tapered slowly rather than discontinued abruptly when ZORprin® (aspirin) is made a part of the treatment program. Patients receiving large doses of aspirin and/or prolonged therapy may develop mild salicylate intoxication (salicylism) that may be reversed by reduction in dosage. Salicylates can produce changes in thyroid function tests. Salicylates should be used with caution in patients with severe hepatic damage, preexisting hypoprothrombinemia, vitamin K deficiency and in those undergoing surgery. Since aspirin release from ZORprin® is pH dependent, it may change in those conditions where the gastric pH has been increased via antacids, gastric secretion inhibitors or surgical procedures. ▫ **ADVERSE REACTIONS**: **Hematologic**: Aspirin interferes with blood clotting. Patients with a history of blood coagulation defects or receiving anti-coagulant drugs or with severe anemia should avoid ZORprin®. Aspirin used chronically may cause a persistent iron deficiency anemia. **Gastrointestinal**: Aspirin may potentiate peptic ulcer, and cause stomach distress or heartburn. Aspirin can cause an increase in occult bleeding and in some patients massive gastrointestinal bleeding. However, the greatest release of active drug from ZORprin® is designed to occur in the small intestine over a period of time. This has resulted in less symptomatic gastrointestinal side effects. **Allergic**: Allergic and anaphylactic reactions have been noted when hypersensitive individuals have taken aspirin. The most common allergic reaction to aspirin is the induction of bronchospasm with asthma-like symptoms. Other reactions are hives, rash, angioedema, as well as rhinitis and nasal polyps. Fatal anaphylactic shock, while not common, has been reported. **Central Nervous System**: Taken in overdoses, aspirin provides stimulation which may be manifested by tinnitus. Following initial stimulation, depression of the central nervous system may be noted. **Renal**: Aspirin may rarely cause an increase in the severity of chronic kidney disease. **Hepatic**: High doses of aspirin have been reported to produce reversible hepatic dysfunction. ▫ **OVERDOSAGE**: Overdosage, if it occurs, would produce the usual symptoms of salicylism, tinnitus, vertigo, headache, confusion, drowsiness, sweating, hyperventilation, vomiting or diarrhea. Treatment for mild intoxication, emptying the stomach with an emetic, or gastric lavage with 5% sodium bicarbonate. Individuals suffering from severe intoxication should, in addition, have forced diuresis by intravenous infusions of saline and sodium bicarbonate or sodium lactate, dextrose solution. In extreme cases, hemodialysis or peritoneal dialysis may be required. ▫ **HOW SUPPLIED**: ZORprin® tablets 800 mg, plain, white capsule-shaped tablets. Bottles of 100 tablets. ▫ **CAUTION**: Federal Law prohibits dispensing without prescription. Manufactured and distributed by Boots Pharmaceuticals, Inc., Shreveport, LA., 71106 USA

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(Continued from Page 745)

EPITOMES—IMPORTANT ADVANCES IN CLINICAL MEDICINE

Urology

Items of progress in urology. Each item in the judgment of a panel of knowledgeable physicians has recently become reasonably firmly established, both as to scientific fact and important clinical significance.

820 **New Forms of Treatment in Cases of Urinary Stone Disease**
GEORGE W. DRACH, MD

820 **Renal Transplantation**
DONALD C. MARTIN, MD

821 **Endourology**
ROBERT I. KAHN, MD

821 **Magnetic Resonance Imaging and Other Radiologic Advances in Urology**
MICHAEL F. SMOLIN, MD

822 **Treatment of Cancer of the Prostate**
ROBERT P. GIBBONS, MD

822 **New Uses of Lasers in Urology**
ALLAN M. SHANBERG, MD

823 **Cancer of Testis Curable**
JOSEPH B. HART, MD

823 **Needle Urethral-Vesical Suspensions for Stress Incontinence**
DAVID R. STASKIN, MD, and SHLOMO RAZ, MD

824 **Infertility—Evaluation and Management**
CAPPY MILES ROTHMAN

824 **Noninvasive Evaluation of Scrotal Masses**
JOSEPH B. HART, MD

824 **Advances in Pediatric Urology**
JEFFREY KAUFMAN, MD

EDITORIALS

826 **Confrontation, Competition or Cooperation**

826 **Neurological Paraneoplastic Syndromes**
STUART A. SCHNECK, MD
Dr Schneck is Professor of Neurology and Neuropathology, University of Colorado School of Medicine, Denver.

828 **Doctors Versus Lawyers—A Crucial Battle Has Been Joined in California**

CASE REPORTS

829 **Multifocal Eosinophilic Granuloma With a Pituitary Stalk Lesion**
ANATOLY LANGER, MD, and IVY FETTES, PhD, MD
From the Department of Medicine, Sunnybrook Medical Centre, University of Toronto Faculty of Medicine, Toronto.

831 **Kaposi's Sarcoma Presenting as Homogeneous Pulmonary Infiltrates in a Patient With Acquired Immunodeficiency Syndrome**
LLOYD RUCKER, MD, and JOSEPHINE MEADOR, MD
From the Department of Medicine, Division of General Internal Medicine and Primary Care, California College of Medicine, University of California Irvine Medical Center, Orange.

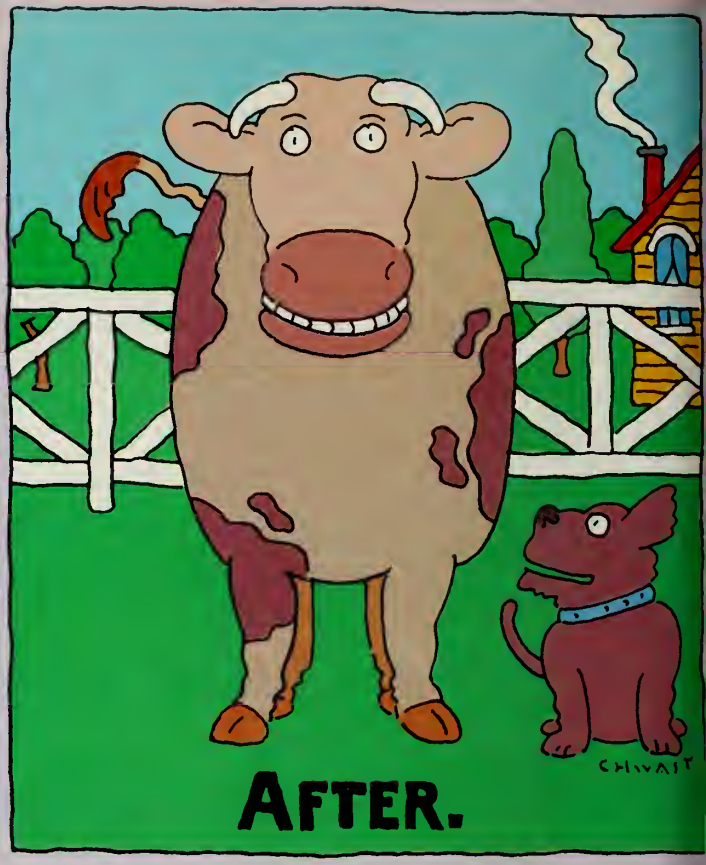
CORRESPONDENCE

834 **Management of Stroke**
KAJ H. JOHANSEN, MD, PhD

835 **Type II Diabetes Mellitus**
MAYER B. DAVIDSON, MD

(Continued on Page 762)

"My great, great, great, great grand daddy."



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This listing of continuing education programs in California, Hawaii and Nevada is supplied by the Committee on Continuing Medical Education of the California Medical Association. All courses and meetings listed have been approved for Category I credit toward the CMA Certificate in Continuing Medical Education. To have accredited courses listed here, please send information at least two months in advance to Department of Continuing Medical Education, California Medical Association, 44 Gough St., San Francisco 94103; or phone (415) 863-5522. For a list of organizations approved for Category I credit toward the CMA Certificate in Continuing Medical Education or for more information on accreditation or certification, please write to the above address.

ALLERGY AND IMMUNOLOGY

August 16-18—**Summer Conference on Allergy, Rheumatology and Orthopedic Surgery.** Scripps Clinic & Research Foundation at Sherwood Hall, La Jolla Museum of Contemporary Art, La Jolla. Friday-Sunday. 14 hrs. Fee: $25-$195. Contact: Bonny A. Mower, Scripps Clinic & Research Foundation, 10666 N. Torrey Pines Rd., La Jolla, CA 92037.

KEY TO ABBREVIATIONS

CMA: California Medical Association
Contact: Continuing Medical Education, California Medical Association, 44 Gough Street, San Francisco 94103. (415) 863-5522.

DREW: Charles R. Drew Postgraduate Medical School
Contact: Flora Harlee-Cordett, MS, MPH, Office of Continuing Education, Charles R. Drew Postgraduate Medical School, 1621 East 120th Street, Los Angeles 90059. (213) 603-3183.

LLU: Loma Linda University
Contact: Varner J. Johns, Jr., MD, Associate Dean for Continuing Medical Education, Loma Linda University School of Medicine, Loma Linda 92354. (714) 796-7311, ext. 2400.

PMC: Pacific Medical Center
Contact: Continuing Education, Pacific Medical Center, PO Box 7999, San Francisco 94120. (415) 563-4321, ext. 2761.

STAN: Stanford University
Contact: Edward Rubenstein, MD, Associate Dean for Postgraduate Education, Stanford University School of Medicine, 300 Pasteur Drive, Stanford 94305. (415) 497-5594.

UCD: University of California, Davis
Contact: Ruth Feryok, Director, Office of Continuing Medical Education, University of California, Davis, School of Medicine, Davis 95616. (916) 752-0328.

UCI: University of California, Irvine
Contact: E. R. Jennings, MD, Assistant Dean, University of California, Irvine, California College of Medicine, c/o UCI/CME Program, Memorial Hospital Medical Center, 2801 Atlantic Avenue, Long Beach 90801. (213) 595-3837, or (714) 856-5414, UCI Extension.

UCLA: University of California, Los Angeles
Contact: Martin D. Shickman, MD, Director, Continuing Education in Medicine and the Health Sciences, PO Box 24902, UCLA, Los Angeles 90024. (213) 825-7241.

UCSD: University of California, San Diego
Contact: Office of Continuing Medical Education, University of California, San Diego, School of Medicine (M-017), La Jolla 92093. (619) 452-3940.

UCSF: University of California, San Francisco
Contact: David S. Gullion, MD, Director, Extended Programs in Medical Education, School of Medicine, University of California, San Francisco 94143. (415) 666-4251.

USC: University of Southern California
Contact: Phil R. Manning, MD, Associate Dean, Postgraduate Division, University of Southern California School of Medicine, 2025 Zonal Avenue, Los Angeles 90033. (213) 224-7051.

ANESTHESIOLOGY

August 8-11—**Clinical Neuroanesthesia Conference.** UCSD at Hotel Intercontinental, San Diego. Thursday-Sunday. 22 hrs.

CARDIOLOGY

June 16-20—**Western Thoracic Surgical Association Annual Meeting** at Hyatt Lake Tahoe, Incline Village. Sunday-Thursday. Contact: WTSA, 13 Elm St., Manchester, MA 01944. (617) 927-8330.

June 21-23—**Diagnosis and Management of the Acute M.I.** International Medical Education Corp. at Hyatt Regency, Lake Tahoe. Friday-Sunday. 13 hrs. Fee: $295. Contact: IMEC, 64 Inverness Dr. E., Englewood, CO 80112.

June 25-27—**Vascular and Pulmonary Disease: Diagnosis and Management.** Medical Education Resources at Balboa Bay Club, Newport Beach. Tuesday-Thursday. 13 hrs. Fee: $275. Contact: Mrs Leslie Shaffer, Medical Education Resources, 5808 S. Rapp St., Ste. 202, Littleton, CO 80120. (303) 798-9682.

June 26-28—**Consultative Cardiology: Update in Diagnostic and Therapeutic Techniques.** American College of Cardiology at Westin South Coast Plaza, Costa Mesa. Wednesday-Friday. Contact: American College of Cardiology, 9111 Old Georgetown Rd., Bethesda, MD 20814.

June 28-30—**ECG Interpretation and Arrhythmia Management.** International Medical Education Corp. at Disneyland Hotel, Anaheim. Friday-Sunday. 13 hrs. Fee: $295. Contact: IMEC, 64 Inverness Dr. E, Englewood, CO 80112.

July 1-3—**Cardiac Morphology: Angiographic, Auscultatory, Echocardiographic and Electrocardiographic Correlations.** American College of Cardiology at Incline Village, Nevada. Monday-Wednesday. Contact: American College of Cardiology, 9111 Old Georgetown Rd., Bethesda, MD 20814.

July 13-20—**Cardiovascular Med. & Surgery & Critical Care Medicine.** Stanford University at Mauna Kea Beach Hotel, Kamuela, Hawaii. Saturday-Saturday.

July 19-21—**Cardiovascular Fitness Sports Medicine and Nutrition.** Mercy Medical Center, Redding.

(Continued on Page 761)

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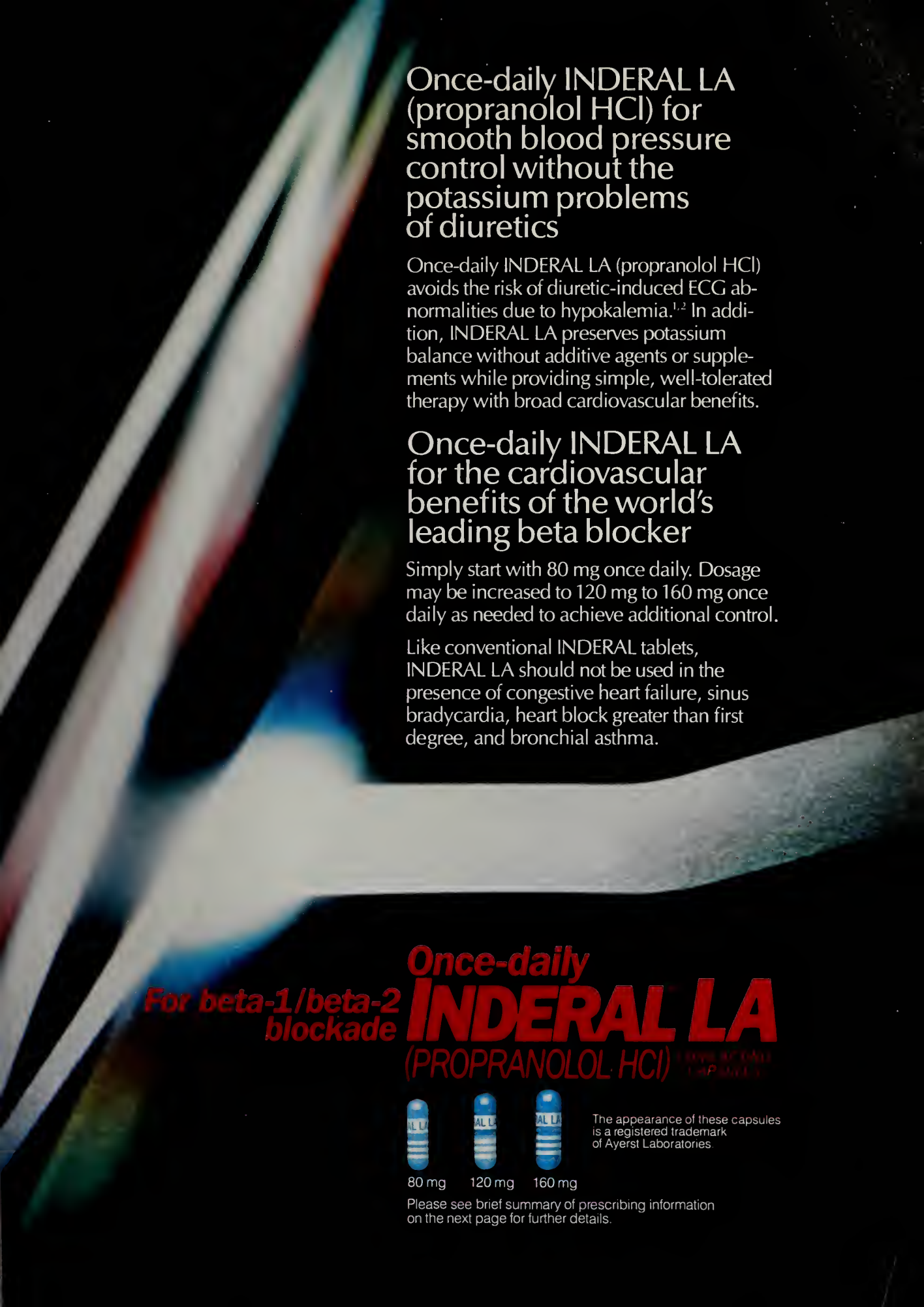

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Like conventional INDERAL tablets, INDERAL LA should not be used in the presence of congestive heart failure, sinus bradycardia, heart block greater than first degree, and bronchial asthma.

For beta-1/beta-2 blockade

Once-daily

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(PROPRANOLOL HCl)

80 mg 120 mg 160 mg

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Please see brief summary of prescribing information on the next page for further details.

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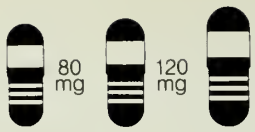

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BRIEF SUMMARY *(FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE CIRCULAR.)*

INDERAL® LA brand of propranolol hydrochloride **(Long Acting Capsules)**

DESCRIPTION. Inderal LA is formulated to provide a sustained release of propranolol hydrochloride. Inderal LA is available as 80 mg, 120 mg, and 160 mg capsules.

CLINICAL PHARMACOLOGY. INDERAL is a nonselective beta-adrenergic receptor blocking agent possessing no other autonomic nervous system activity. It specifically competes with beta-adrenergic receptor stimulating agents for available receptor sites. When access to beta-receptor sites is blocked by INDERAL, the chronotropic, inotropic, and vasodilator responses to beta-adrenergic stimulation are decreased proportionately.

INDERAL LA Capsules (80, 120, and 160 mg) release propranolol HCl at a controlled and predictable rate. Peak blood levels following dosing with INDERAL LA occur at about 6 hours and the apparent plasma half-life is about 10 hours. When measured at steady state over a 24-hour period the areas under the propranolol plasma concentration-time curve (AUCs) for the capsules are approximately 60% to 65% of the AUCs for a comparable divided daily dose of INDERAL tablets. The lower AUCs for the capsules are due to greater hepatic metabolism of propranolol, resulting from the slower rate of absorption of propranolol. Over a twenty-four (24) hour period, blood levels are fairly constant for about twelve (12) hours then decline exponentially.

INDERAL LA should not be considered a simple mg for mg substitute for conventional propranolol and the blood levels achieved do not match (are lower than) those of two to four times daily dosing with the same dose. When changing to INDERAL LA from conventional propranolol, a possible need for retitration upwards should be considered especially to maintain effectiveness at the end of the dosing interval. In most clinical settings, however, such as hypertension or angina where there is little correlation between plasma levels and clinical effect, INDERAL LA has been therapeutically equivalent to the same mg dose of conventional INDERAL as assessed by 24-hour effects on blood pressure and on 24-hour exercise responses of heart rate, systolic pressure and rate pressure product. INDERAL LA can provide effective beta blockade for a 24-hour period.

The mechanism of the antihypertensive effect of INDERAL has not been established. Among the factors that may be involved in contributing to the antihypertensive action are (1) decreased cardiac output, (2) inhibition of renin release by the kidneys, and (3) diminution of tonic sympathetic nerve outflow from vasomotor centers in the brain. Although total peripheral resistance may increase initially, it readjusts to or below the pretreatment level with chronic use. Effects on plasma volume appear to be minor and somewhat variable. INDERAL has been shown to cause a small increase in serum potassium concentration when used in the treatment of hypertensive patients.

In angina pectoris, propranolol generally reduces the oxygen requirement of the heart at any given level of effort by blocking the catecholamine-induced increases in the heart rate, systolic blood pressure, and the velocity and extent of myocardial contraction. Propranolol may increase oxygen requirements by increasing left ventricular fiber length, end diastolic pressure and systolic ejection period. The net physiologic effect of beta-adrenergic blockade is usually advantageous and is manifested during exercise by delayed onset of pain and increased work capacity.

In dosages greater than required for beta blockade, INDERAL also exerts a quinidine-like or anesthetic-like membrane action which affects the cardiac action potential. The significance of the membrane action in the treatment of arrhythmias is uncertain.

The mechanism of the antimigraine effect of propranolol has not been established. Beta-adrenergic receptors have been demonstrated in the pial vessels of the brain.

Beta receptor blockade can be useful in conditions in which, because of pathologic or functional changes, sympathetic activity is detrimental to the patient. But there are also situations in which sympathetic stimulation is vital. For example, in patients with severely damaged hearts, adequate ventricular function is maintained by virtue of sympathetic drive which should be preserved. In the presence of AV block, greater than first degree, beta blockade may prevent the necessary facilitating effect of sympathetic activity on conduction. Beta blockade results in bronchial constriction by interfering with adrenergic bronchodilator activity which should be preserved in patients subject to bronchospasm.

Propranolol is not significantly dialyzable.

INDICATIONS AND USAGE. Hypertension: INDERAL LA is indicated in the management of hypertension; it may be used alone or used in combination with other antihypertensive agents, particularly a thiazide diuretic. INDERAL LA is not indicated in the management of hypertensive emergencies.

Angina Pectoris Due to Coronary Atherosclerosis: INDERAL LA is indicated for the long-term management of patients with angina pectoris.

Migraine: INDERAL LA is indicated for the prophylaxis of common migraine headache. The efficacy of propranolol in the treatment of a migraine attack that has started has not been established and propranolol is not indicated for such use.

Hypertrophic Subaortic Stenosis: INDERAL LA is useful in the management of hypertrophic subaortic stenosis, especially for treatment of exertional or other stress-induced angina, palpitations, and syncope. INDERAL LA also improves exercise performance. The effectiveness of propranolol hydrochloride in this disease appears to be due to a reduction of the elevated outflow pressure gradient which is exacerbated by beta-receptor stimulation. Clinical improvement may be temporary.

CONTRAINDICATIONS. INDERAL is contraindicated in 1) cardiogenic shock, 2) sinus bradycardia and greater than first degree block, 3) bronchial asthma, 4) congestive heart failure (see WARNINGS) unless the failure is secondary to a tachyarrhythmia treatable with INDERAL.

WARNINGS. CARDIAC FAILURE. Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta blockade may precipitate more severe failure. Although beta blockers should be avoided in overt congestive heart failure, if necessary, they can be used with close follow-up in patients with a history of failure who are well compensated and are receiving digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle.

IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta blockers can, in some cases, lead to cardiac failure. Therefore, at the first sign or symptom of heart failure, the patient should be digitalized and/or treated with diuretics, and the response observed closely; or INDERAL should be discontinued (gradually, if possible).

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following abrupt discontinuance of INDERAL therapy. Therefore, when discontinuance of INDERAL is planned the dosage should be gradually reduced over at least a few weeks, and the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications.

Nonallergic Bronchospasm (e.g., chronic bronchitis, emphysema)— PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

MAJOR SURGERY. The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

INDERAL (propranolol HCl), like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, e.g., dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in starting and maintaining the heartbeat has also been reported with beta blockers.

DIABETES AND HYPOGLYCEMIA. Beta-adrenergic blockade may prevent the appearance of certain premonitory signs and symptoms (pulse rate and pressure changes) of acute hypoglycemia in labile insulin-dependent diabetes. In these patients, it may be more difficult to adjust the dosage of insulin.

THYROTOXICOSIS. Beta blockade may mask certain clinical signs of hyperthyroidism. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. Propranolol does not distort thyroid function tests.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

PRECAUTIONS. *General.* Propranolol should be used with caution in patients with impaired hepatic or renal function. INDERAL (propranolol HCl) is not indicated for the treatment of hypertensive emergencies.

Beta adrenoreceptor blockade can cause reduction of intraocular pressure. Patients should be told that INDERAL may interfere with the glaucoma screening test. Withdrawal may lead to a return of increased intraocular pressure.

Clinical Laboratory Tests. Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

DRUG INTERACTIONS. Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if INDERAL is administered. The added catecholamine-blocking action may produce an excessive reduction of resting sympathetic nervous activity which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension.

Carcinogenesis, Mutagenesis, Impairment of Fertility. Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In 18-month studies in both rats and mice, employing doses up to 150 mg/kg/day, there was no evidence of significant drug-induced toxicity. There were no drug-related tumorigenic effects at any of the dosage levels. Reproductive studies in animals did not show any impairment of fertility that was attributable to the drug.

Pregnancy. Pregnancy Category C. INDERAL has been shown to be embryotoxic in animal studies at doses about 10 times greater than the maximum recommended human dose.

There are no adequate and well-controlled studies in pregnant women. INDERAL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. INDERAL is excreted in human milk. Caution should be exercised when INDERAL is administered to a nursing woman.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS. Most adverse effects have been mild and transient and have rarely required the withdrawal of therapy.

Cardiovascular: bradycardia, congestive heart failure, intensification of AV block, hypotension, paresthesia of hands, thrombocytopenic purpura, arterial insufficiency, usually of the Raynaud type.

Central Nervous System: lightheadedness; mental depression manifested by insomnia, lassitude, weakness, fatigue, reversible mental depression progressing to catatonia, visual disturbances, hallucinations, an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics.

Gastrointestinal: nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis.

Allergic: pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm and respiratory distress.

Respiratory: bronchospasm.

Hematologic: agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Auto-Immune: In extremely rare instances, systemic lupus erythematosus has been reported.

Miscellaneous: alopecia, LE-like reactions, psoriasiform rashes, dry eyes, male impotence, and Peyronie's disease have been reported rarely. Oculomucocutaneous reactions involving the skin, serous membranes and conjunctivae reported for a beta blocker (practolol) have not been associated with propranolol.

DOSAGE AND ADMINISTRATION. INDERAL LA provides propranolol hydrochloride in a sustained-release capsule for administration once daily. If patients are switched from INDERAL tablets to INDERAL LA capsules, care should be taken to assure that the desired therapeutic effect is maintained. INDERAL LA should not be considered a simple mg for mg substitute for INDERAL. INDERAL LA has different kinetics and produces lower blood levels. Retitration may be necessary especially to maintain effectiveness at the end of the 24-hour dosing interval.

HYPERTENSION—*Dosage must be individualized.* The usual initial dosage is 80 mg INDERAL LA once daily, whether used alone or added to a diuretic. The dosage may be increased to 120 mg once daily or higher until adequate blood pressure control is achieved. The usual maintenance dosage is 120 to 160 mg once daily. In some instances a dosage of 640 mg may be required. The time needed for full hypertensive response to a given dosage is variable and may range from a few days to several weeks.

ANGINA PECTORIS—*Dosage must be individualized.* Starting with 80 mg INDERAL LA once daily, dosage should be gradually increased at three to seven day intervals until optimum response is obtained. Although individual patients may respond at any dosage level, the average optimum dosage appears to be 160 mg once daily. In angina pectoris, the value and safety of dosage exceeding 320 mg per day have not been established.

If treatment is to be discontinued, reduce dosage gradually over a period of a few weeks (see WARNINGS).

MIGRAINE—*Dosage must be individualized.* The initial oral dose is 80 mg INDERAL LA once daily. The usual effective dose range is 160-240 mg once daily. The dosage may be increased gradually to achieve optimum migraine prophylaxis. If a satisfactory response is not obtained within four to six weeks after reaching the maximum dose, INDERAL LA therapy should be discontinued. It may be advisable to withdraw the drug gradually over a period of several weeks.

HYPERTROPHIC SUBAORTIC STENOSIS—80-160 mg INDERAL LA once daily.

PEDIATRIC DOSAGE—At this time the data on the use of the drug in this age group are too limited to permit adequate directions for use.

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1. Holland OB, Nixon JV, Kuhnert L: Diuretic-induced ventricular ectopic activity. *Am J Med* 1981;70:762-768. **2.** Holme I, Helgeland A, Hjermann I, et al: Treatment of mild hypertension with diuretics. The importance of ECG abnormalities in the Oslo study and in MRFIT. *JAMA* 1984;251:1298-1299.

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Friday-Sunday. Fee: $100. Contact: Shelly Underwood, Mercy Medical Center, PO Box 6009, Redding 96099. (916) 243-2121.

July 19-21—**Coronary Artery Disease and Sudden Death: Primary and Secondary Prevention.** International Medical Education Corp. at Marriott Hotel, Newport Beach, CA. Friday-Sunday. 13 hours. Fee: $295. Contact: IMEC, 64 Inverness Dr. E., Englewood, CO 80112.

July 29-August 3—**Doppler and 2-D Echocardiography.** The Institute for Medical Studies at Anaheim. Monday-Saturday. 33 hrs. Contact: Kim Stroich, IMS, 30131 Town Center Dr., Ste. 215, Laguna Niguel, CA 92677. (714) 494-4499.

August 2-4—**Vascular and Pulmonary Disease: Diagnosis and Management.** University of Colorado at Disneyland Hotel, Anaheim. Friday-Sunday. 13 hrs. Contact: Medical Education Resources, 5808 S. Rapp St., Ste. 202, Littleton, CO 80120. (800) 421-3756.

August 11-16—**Current Concepts in Cardiology.** UCD at Hyatt Lake Tahoe, Incline Village, NV. Sunday-Friday.

EMERGENCY MEDICINE

June 20-21—**6th Annual Trauma Seminar.** Charles R. Drew Postgraduate Medical School at Disneyland Hotel, Anaheim. Thursday-Friday. 16 hrs. Contact: Dr. S. Bala, (213) 603-4510.

June 24-28—**Postgraduate Institute for Emerg. Physicians, Symposium 111.** UCSD at Hanalei Hotel, San Diego. Monday-Friday. 13-36 hrs. Fee: $200-675.

June 27-30—**Update in Emergency Medicine.** Mercy Medical Center, Redding at Salmon River (Whitewater rafting trip). Thursday-Sunday. 10 hrs. Fee: $125. Contact: Shelly Underwood, Mercy Medical Center, Redding, PO Box 6009, Redding, CA 96099-6009. (916) 243-2121.

July 3-6—**Wilderness Emergency Care.** Mercy Medical Center, Redding. Wednesday-Saturday. 10 hrs. Fee: $125. Contact: Shelly Underwood, Mercy Medical Center, PO Box 6009, Redding, CA 96099. (916) 243-2121.

July 12-14—**Update in Emergency Medicine.** Mercy Medical Center, Redding. Friday-Sunday. 10 hrs. Fee: $100. Contact: Shelly Underwood, Mercy Medical Center, PO Box 6009, Redding, CA 96099. (916) 243-2121.

August 12-16—**Wilderness Medicine.** UCSD at Lake Tahoe, NV. Monday-Friday. 23 hrs.

August 26-30—**Topics in Emergency Medicine.** UCSF at Holiday Inn on Union Square, San Francisco. Monday-Friday. 33 hrs.

INTERNAL MEDICINE

June 19-21—**Gastroenterology: Recent Developments in Theory and Practice.** UCSF at Mark Hopkins Hotel, San Francisco. Wednesday-Friday. Fees: $375.

June 21-23—**California Society of Internal Medicine—Annual Meeting** at Hotel Del Coronado, Coronado. Friday-Sunday. 3 hrs. Contact: Carol Holland Parlette, CSIM, 703 Market Street, San Francisco 94103.

June 24-28—**Advances in Internal Medicine.** UCSF at Hotel Meridien, San Francisco. Fee: $420.

August 18-23—**New Advances in Internal Medicine: Clinical Applications.** UCD at Hyatt Regency, Monterey. Sunday-Friday.

August 31-September 3—**Advances in Internal Medicine Postgraduate Course 1985.** UCSD at Sheraton Harbor Island East, San Diego. Saturday-Tuesday. 25 hrs.

OPHTHALMOLOGY

June 29-July 3—**Pacific Coast Oto-Ophthalmological Society Annual Meeting** at Hotel Del Coronado, Coronado. Saturday-Wednesday. Contact: Rober-Christensen, MD, UCLA Med Center, 800 Westwood Plaza, Los Angeles, CA 90024.

PEDIATRICS

June 21-22—**Pediatric Pulmonary Update—1985.** Children's Hospital and Health Center at San Diego Hilton Beach and Tennis Resort. Friday-Saturdy. Contact: Sung Min Park, MD, Children's Hospital and Health Center, 8001 Frost St., San Diego 92123. (619) 576-5854.

June 22-29—**3rd National Kaiser Permanente Pediatrics Conference** at Maui, Hawaii. One Week. 22.5 hrs. Fee: $100. Contact: Steven Black, MD (45) 428-5815.

July 5-7—**Pediatrics for the Practitioner.** American Academy of Pediatrics at Anaheim. Friday-Sunday. 13 hrs. Fee: $225. Contact: Eve Black, PO Box 2134, Inglewood, CA 90305.

RADIOLOGY

August 27-30—**Radiology Conference.** Northern California Radiology Society at Napa Valley. Tuesday-Friday. 20 hrs. Fee: $275-$345. Contact: Sacramento Radiology Research & Education Foundation, PO Box 18184, Sacramento, CA 95819.

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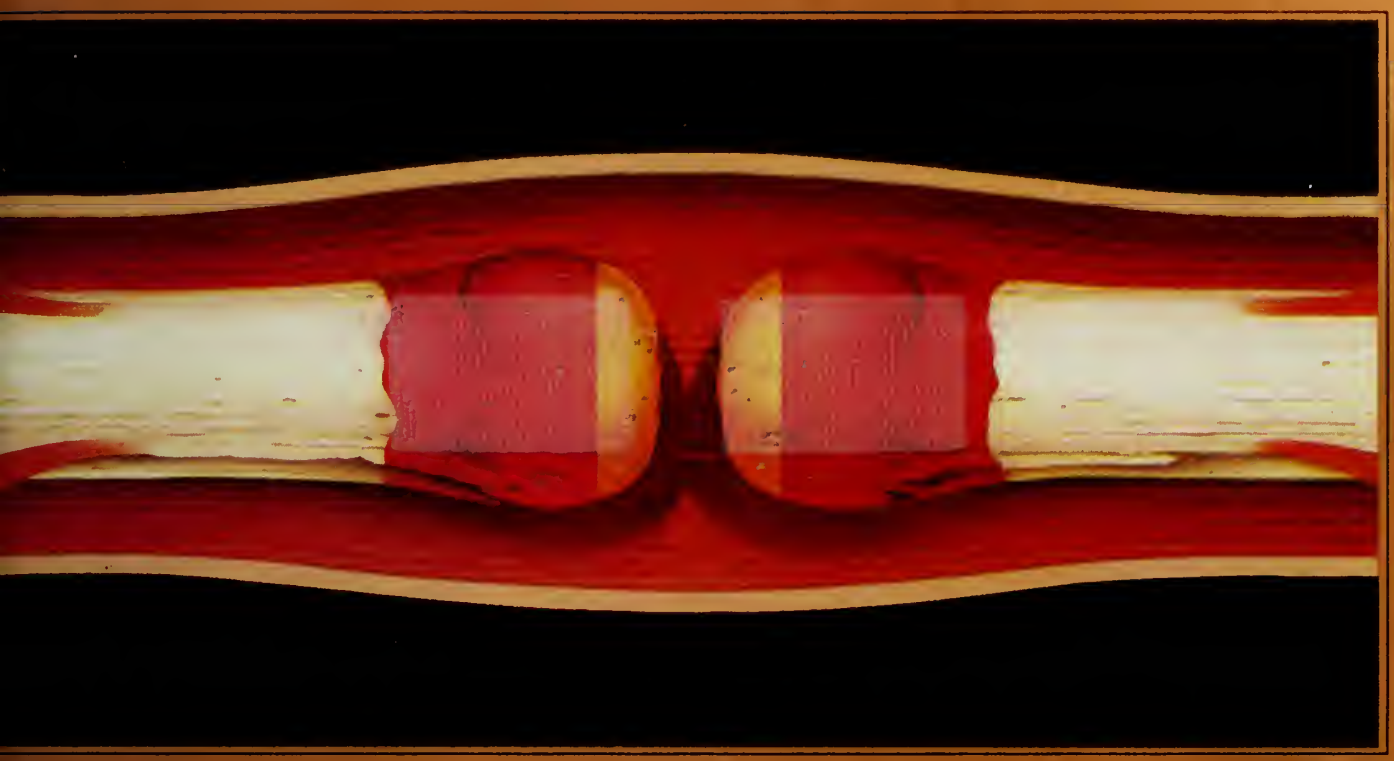

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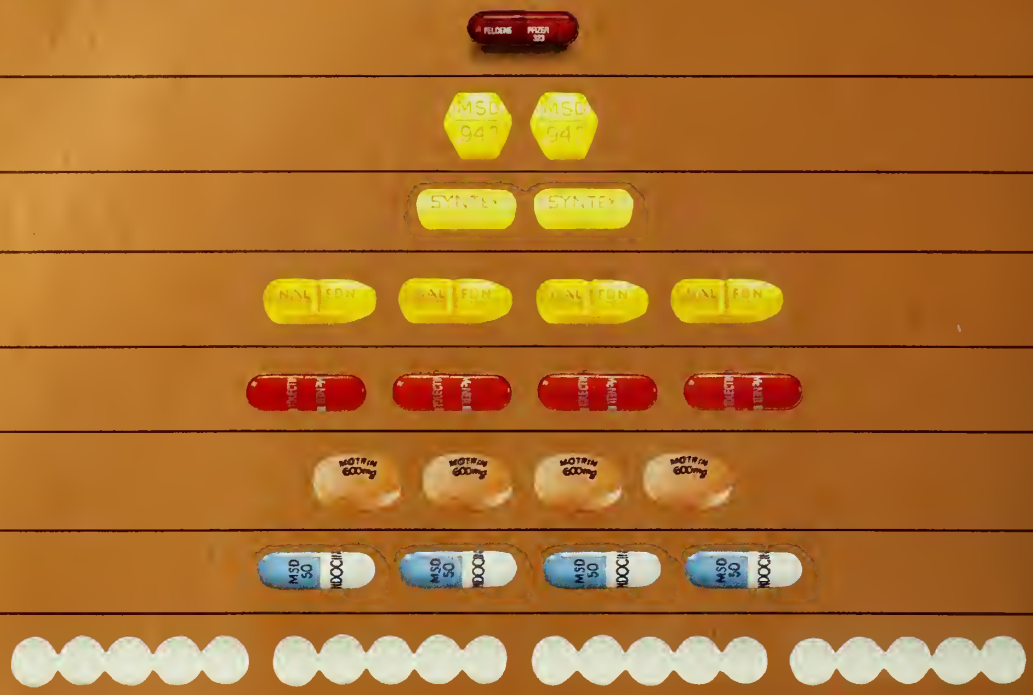

Source: PDR, 1985, Manufacturers' Prescribing Information

Indicates maximum dosage for osteoarthritis and rheumatoid arthritis for the antiarthritic agents included. Consult manufacturers' prescribing information.

Brief Summary

FELDENE® (piroxicam) Capsules

CONTRAINDICATIONS: FELDENE (piroxicam) should not be used in patients who have previously exhibited hypersensitivity to it, or in individuals with the syndrome comprised of bronchospasm, nasal polyps and angioedema precipitated by aspirin or other nonsteroidal anti-inflammatory drugs.

WARNINGS: Peptic ulceration, perforation and G.I. bleeding—sometimes severe, and, in some instances fatal—have been reported with patients receiving FELDENE. If FELDENE must be given to patients with a history of upper gastrointestinal tract disease, the patient should be under close supervision (see ADVERSE REACTIONS).

PRECAUTIONS: As with other anti-inflammatory agents, long-term administration to animals results in renal papillary necrosis and related pathology in rats, mice and dogs.

Acute renal failure and hyperkalemia as well as reversible elevations of BUN and serum creatinine have been reported with FELDENE. In addition to reversible changes in renal function, interstitial nephritis, glomerulitis, papillary necrosis and the nephrotic syndrome have been reported with FELDENE.

Although other nonsteroidal anti-inflammatory drugs do not have the same direct effect on platelets that aspirin does, all drugs inhibiting prostaglandin biosynthesis do interfere with platelet function to some degree.

Because of reports of adverse eye findings with nonsteroidal anti-inflammatory agents, it is recommended that patients who develop visual complaints during treatment with FELDENE have ophthalmic evaluation.

As with other nonsteroidal anti-inflammatory drugs, borderline elevations of one or more liver tests may occur in up to 15% of patients. A patient with symptoms and/or signs suggesting liver dysfunction, or in whom abnormal liver tests have occurred, should be evaluated for evidence of the development of more severe hepatic reaction while on therapy with FELDENE.

Severe hepatic reactions, including jaundice and cases of fatal hepatitis have been reported with FELDENE. Although such reactions are rare, if abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), FELDENE should be discontinued. (See also ADVERSE REACTIONS.)

Although at the recommended dose of 20 mg/day of FELDENE increased fecal blood loss due to gastrointestinal irritation did not occur, in about 4% of the patients treated with FELDENE alone or concomitantly with aspirin, reductions in hemoglobin and hematocrit values were observed.

Peripheral edema has been observed in approximately 2% of the patients treated with FELDENE. Therefore, FELDENE should be used with caution in patients with heart failure, hypertension or other conditions predisposing to fluid retention.

A combination of dermatological and/or allergic signs and symptoms suggestive of serum sickness have occasionally occurred in conjunction with the use of FELDENE. These include arthralgias, pruritus, fever, fatigue, and rash including vesiculo bullous reactions and exfoliative dermatitis.

DRUG INTERACTIONS: Interactions with coumarin-type anticoagulants have been reported with FELDENE since marketing. Therefore, physicians should closely monitor patients for a change in dosage requirements when administering FELDENE to patients on coumarin-type anticoagulants and other highly protein-bound drugs.

Plasma levels of piroxicam are depressed to approximately 80% of their normal values when FELDENE is administered in conjunction with aspirin (3900 mg/day), but concomitant administration of antacids has no effect on piroxicam plasma levels.

Nonsteroidal anti-inflammatory agents, including FELDENE, have been reported to increase steady state plasma lithium levels. It is recommended that plasma lithium levels be monitored when initiating, adjusting and discontinuing FELDENE.

Carcinogenesis, Chronic Animal Toxicity and Impairment of Fertility: Subacute and chronic toxicity studies have been carried out in rats, mice, dogs, and monkeys.

The pathology most often seen was that characteristically associated with the animal toxicology of anti-inflammatory agents: renal papillary necrosis (see PRECAUTIONS) and gastrointestinal lesions.

In classical studies in laboratory animals, piroxicam did not show any teratogenic potential.

Reproductive studies revealed no impairment of fertility in animals.

Pregnancy and Nursing Mothers: Like other drugs which inhibit the synthesis and release of prostaglandins, piroxicam administration continued late into pregnancy increased the incidence of dystocia and delayed parturition in animals. Gastrointestinal tract toxicity was increased in pregnant females in the last trimester of pregnancy compared to non-pregnant females or females in earlier trimesters of pregnancy.

FELDENE is not recommended for use in nursing mothers or in pregnant women because of the animal findings and since safety for such use has not been established in humans.

Use in Children: Dosage recommendations and indications for use in children have not been established.

ADVERSE REACTIONS: Gastrointestinal symptoms are the most prominent side effects, occurring in approximately 20% of the patients, which in most instances did not interfere with the course of therapy. Of the patients experiencing gastrointestinal side effects, approximately 5% discontinued therapy with an overall incidence of peptic ulceration of about 1%.

Adverse reactions are listed below by body system for all patients in clinical trials with FELDENE at doses of 20 mg/day.

Incidence Greater Than 1%: The following adverse reactions occurred more frequently than 1 in 100.

Gastrointestinal: stomatitis, anorexia, epigastric distress,* nausea,* constipation, abdominal discomfort, flatulence, diarrhea, abdominal pain, indigestion.

Hematological: decreases in hemoglobin* and hematocrit* (see PRECAUTIONS), anemia, leucopenia, eosinophilia.

Dermatologic: pruritus, rash.

Central Nervous System: dizziness, somnolence, vertigo.

Urogenital: BUN and creatinine elevations (see PRECAUTIONS).

Body as a Whole: headache, malaise.

Special Senses: tinnitus.

Cardiovascular/Respiratory: edema (see PRECAUTIONS).

* Reactions occurring in 3% to 9% of patients treated with FELDENE (piroxicam).

Reactions occurring in 1% to 3% of patients are unmarked.

Incidence Less Than 1% (Causal Relationship Probable): The following adverse reactions occurred less frequently than 1 in 100. The probability exists that there is a causal relationship between FELDENE and these reactions.

Gastrointestinal: liver function abnormalities, jaundice, hepatitis (see PRECAUTIONS), vomiting, hematemesis, melena, gastrointestinal bleeding, perforation and ulceration (see WARNINGS), dry mouth.

Hematological: thrombocytopenia, petechial rash, ecchymosis, bone marrow depression including aplastic anemia, epistaxis.

Dermatologic: sweating, erythema, bruising, desquamation, exfoliative dermatitis, erythema multiforme, toxic epidermal necrolysis, Stevens-Johnson syndrome, vesiculo bullous reactions, photoallergic skin reactions.

Central Nervous System: depression, insomnia, nervousness.

Urogenital: hematuria, proteinuria, interstitial nephritis, renal failure, hyperkalemia, glomerulitis, papillary necrosis, nephrotic syndrome (see PRECAUTIONS).

Body as a Whole: pain (colic), fever, flu-like syndrome (see PRECAUTIONS).

Special Senses: swollen eyes, blurred vision, eye irritations.

Cardiovascular/Respiratory: hypertension, worsening of congestive heart failure (see PRECAUTIONS), exacerbation of angina.

Metabolic: hypoglycemia, hyperglycemia, weight increase, weight decrease.

Hypersensitivity: anaphylaxis, bronchospasm, urticaria/angioedema, vasculitis, "serum sickness" (see PRECAUTIONS).

Incidence Less Than 1% (Causal Relationship Unknown): Other adverse reactions were reported with a frequency of less than 1 in 100, but a causal relationship between FELDENE and the reaction could not be determined.

Gastrointestinal: pancreatitis.

Dermatologic: onycholysis, loss of hair.

Central Nervous System: akathisia, hallucinations, mood alterations, dream abnormalities, mental confusion, paresthesias.

Urogenital System: dysuria.

Body as a Whole: weakness.

Cardiovascular/Respiratory: palpitations, dyspnea.

Hypersensitivity: positive ANA.

OVERDOSAGE: In the event treatment for overdosage is required, the long plasma half-life of piroxicam should be considered. The absence of experience with acute overdosage precludes characterization of sequelae and recommendations of specific antidotal efficacy at this time. It is reasonable to assume that the standard measures of gastric evacuation and general supportive therapy would apply. In addition to supportive measures, the use of activated charcoal may effectively reduce the absorption and reabsorption of piroxicam. Experiments in dogs have demonstrated that the use of multiple-dose treatments with activated charcoal could reduce the half-life of piroxicam elimination from 27 hours (without charcoal) to 11 hours and reduce the systemic bioavailability of piroxicam by as much as 37% when activated charcoal is given as late as 6 hours after administration of piroxicam.

ADMINISTRATION AND DOSAGE: Rheumatoid Arthritis, Osteoarthritis. It is recommended that FELDENE therapy be initiated and maintained at a single daily dose of 20 mg. If desired, the daily dose may be divided.

Dosage recommendations and indications for use in children have not been established.

More detailed professional information available on request.

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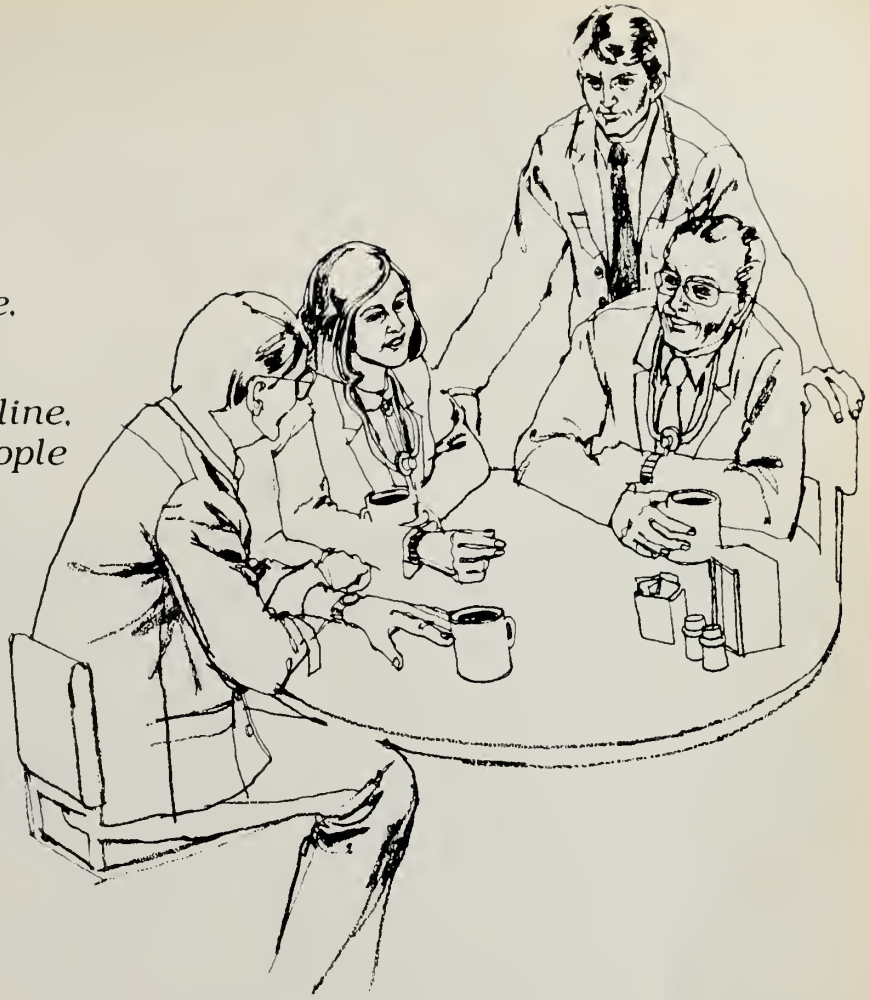

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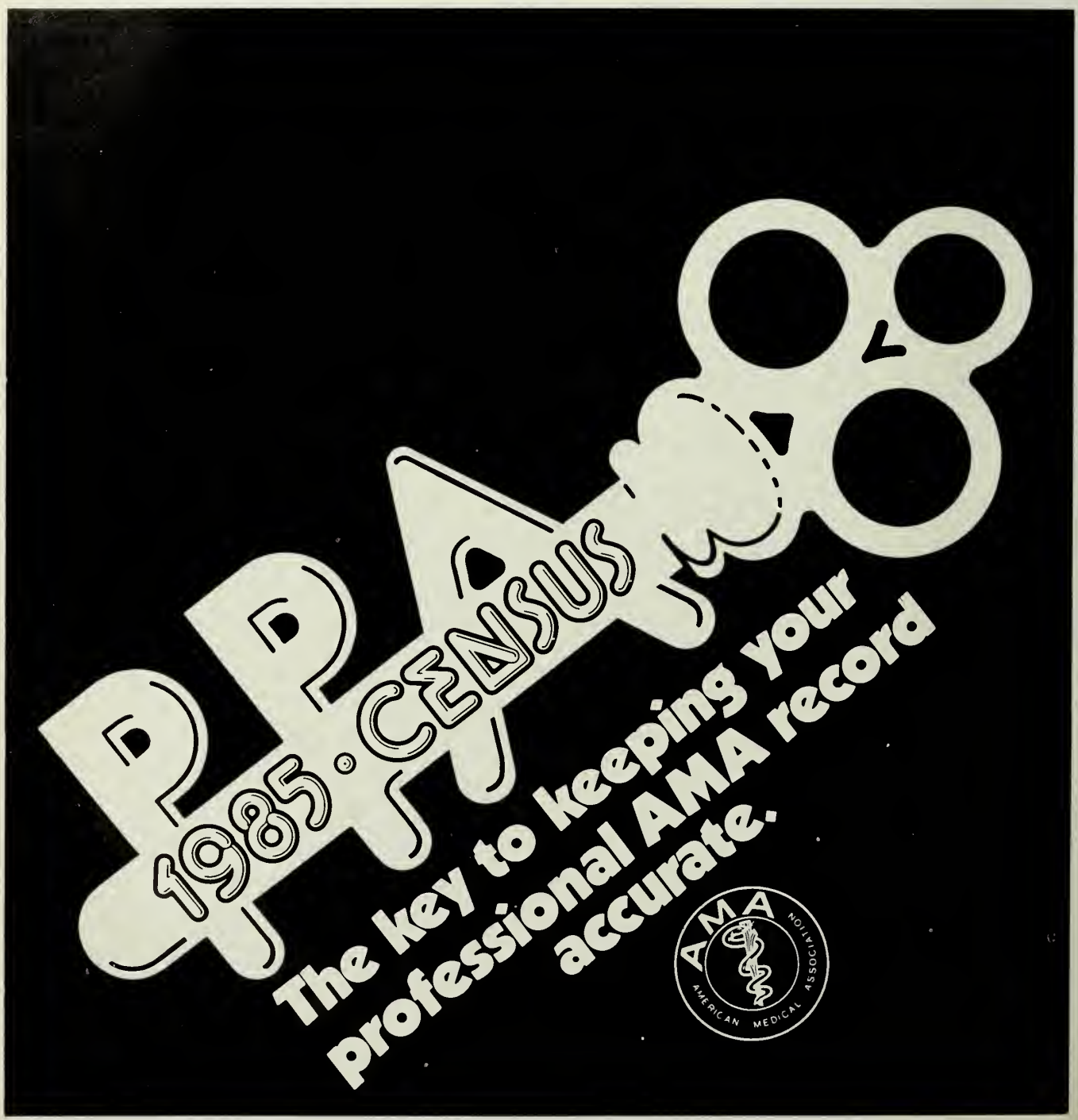

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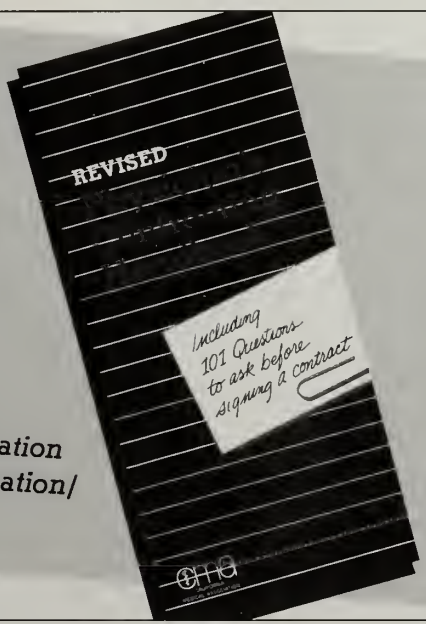

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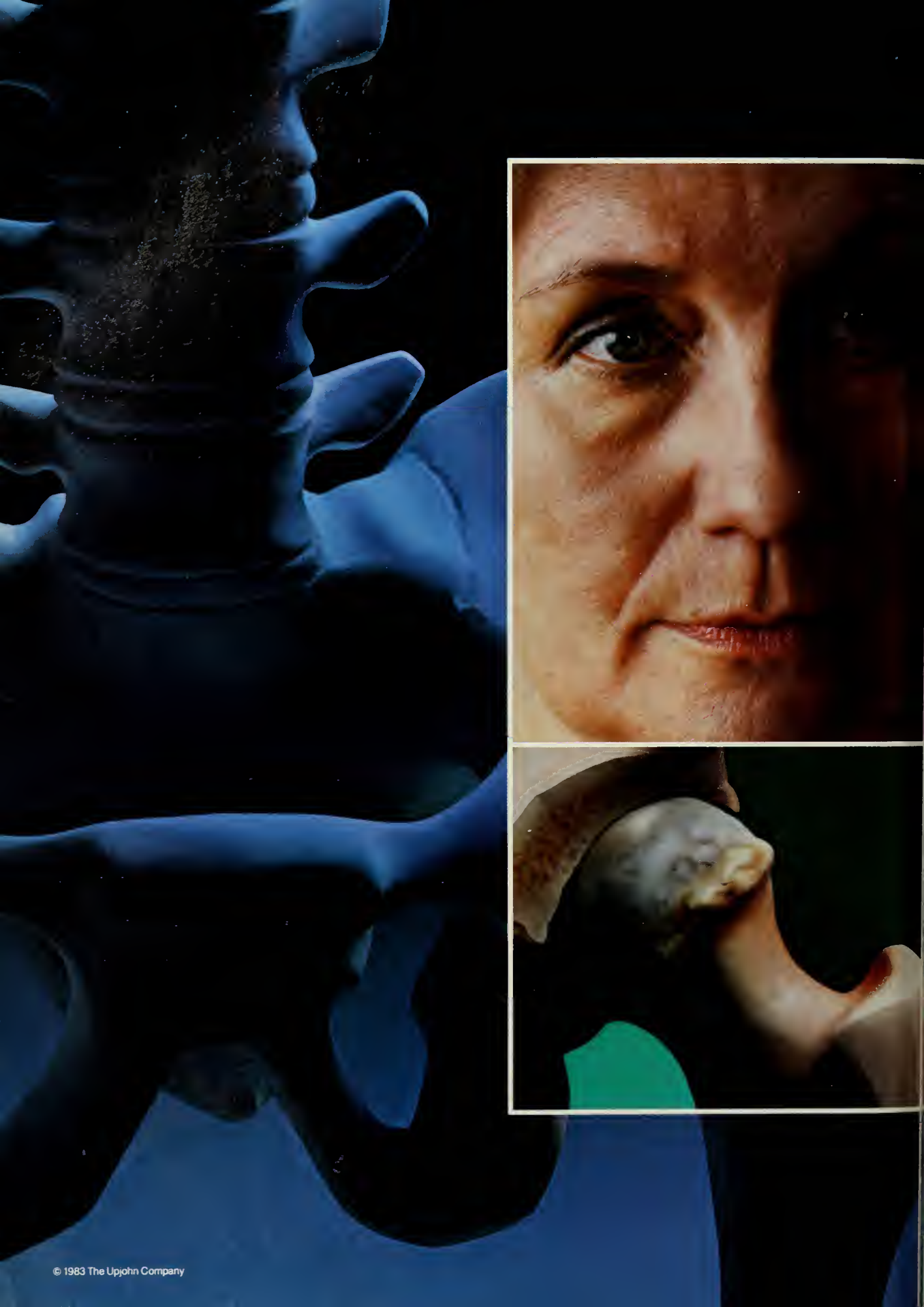

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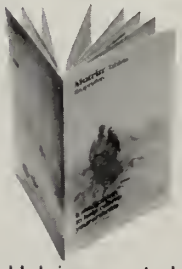

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Contraindications: Anaphylactoid reactions have occurred in individuals hypersensitive to *Motrin* Tablets or with the syndrome of nasal polyps, angioedema and bronchospastic reactivity to aspirin, iodides, or other nonsteroidal anti-inflammatory agents.

Warnings: Peptic ulceration and GI bleeding, sometimes severe, have been reported. Ulceration, perforation and bleeding may end fatally. An association has not been established. Use *Motrin* Tablets under close supervision in patients with a history of upper gastrointestinal tract disease, after consulting ADVERSE REACTIONS. In patients with active peptic ulcer and active rheumatoid arthritis, try nonulcerogenic drugs, such as gold. If *Motrin* Tablets are used, observe the patient closely for signs of ulcer perforation or GI bleeding.

Chronic studies in rats and monkeys have shown mild renal toxicity with papillary edema and necrosis. Renal papillary necrosis has rarely been shown in humans treated with *Motrin* Tablets.

Precautions: Blurred and/or diminished vision, scotomata, and/or changes in color vision have been reported. If these develop, discontinue *Motrin* Tablets and the patient should have an ophthalmologic examination, including central visual fields and color vision testing.

Fluid retention and edema have been associated with *Motrin* Tablets; use with caution in patients with a history of cardiac decompensation or hypertension. In patients with renal impairment, reduced dosage may be necessary. Prospective studies of *Motrin* Tablets safety in patients with chronic renal failure have not been done.

Motrin Tablets can inhibit **platelet aggregation** and prolong bleeding time. Use with caution in persons with intrinsic coagulation defects and on anticoagulant therapy.

Patients should report signs or symptoms of **gastrointestinal ulceration** or bleeding, skin rash, weight gain, or edema.

Patients on prolonged **corticosteroid therapy** should have therapy tapered slowly when *Motrin* Tablets are added.

The antipyretic, anti-inflammatory activity of *Motrin* Tablets may mask inflammation and fever.

As with other nonsteroidal anti-inflammatory drugs, borderline elevations of liver tests may occur in up to 15% of patients. These abnormalities may progress, may remain essentially unchanged, or may be transient with continued therapy. Meaningful elevations of SGPT or SGOT (AST) occurred in controlled clinical trials in less than 1% of patients. Severe hepatic reactions, including jaundice and cases of fatal hepatitis, have been reported with ibuprofen as with other nonsteroidal anti-inflammatory drugs. If liver disease develops or if systemic manifestations occur (e.g. eosinophilia, rash, etc.), *Motrin* should be discontinued.

Drug interactions. *Aspirin:* used concomitantly may decrease *Motrin* blood levels.

Coumarin: bleeding has been reported in patients taking *Motrin* and coumarin.

Pregnancy and nursing mothers: *Motrin* should not be taken during pregnancy or by nursing mothers.

Adverse Reactions: The most frequent type of adverse reaction occurring with *Motrin* is gastrointestinal of which one or more occurred in 4% to 16% of the patients.

Incidence Greater than 1% (but less than 3%)–Probable Causal Relationship

Gastrointestinal: Nausea,* epigastric pain,* heartburn,* diarrhea, abdominal distress, nausea and vomiting, indigestion, constipation, abdominal cramps or pain, fullness of GI tract (bloating and flatulence); **Central Nervous System:** Dizziness,* headache, nervousness; **Dermatologic:** Rash* (including maculopapular type), pruritus; **Special Senses:** Tinnitus; **Metabolic/Endocrine:** Decreased appetite; **Cardiovascular:** Edema, fluid retention (generally responds promptly to drug discontinuation; see PRECAUTIONS).

Incidence less than 1%–Probable Causal Relationship**

Gastrointestinal: Gastric or duodenal ulcer with bleeding and/or perforation, gastrointestinal hemorrhage, melena, gastritis, hepatitis, jaundice, abnormal liver function tests; **Central Nervous System:** Depression, insomnia, confusion, emotional lability, somnolence, aseptic meningitis with fever and coma; **Dermatologic:** Vesiculobullous eruptions, urticaria, erythema multiforme, Stevens-Johnson syndrome, alopecia; **Special Senses:** Hearing loss, amblyopia (blurred and/or diminished vision, scotomata, and/or changes in color vision) (see PRECAUTIONS); **Hematologic:** Neutropenia, agranulocytosis, aplastic anemia, hemolytic anemia (sometimes Coombs positive), thrombocytopenia with or without purpura, eosinophilia, decreases in hemoglobin and hematocrit; **Cardiovascular:** Congestive heart failure in patients with marginal cardiac function, elevated blood pressure, palpitations; **Allergic:** Syndrome of abdominal pain, fever, chills, nausea and vomiting; anaphylaxis; bronchospasm (see CONTRAINDICATIONS); **Renal:** Acute renal failure in patients with pre-existing significantly impaired renal function, decreased creatinine clearance, polyuria, azotemia, cystitis, hematuria; **Miscellaneous:** Dry eyes and mouth, gingival ulcer, rhinitis.

Incidence less than 1%–Causal Relationship Unknown**

Gastrointestinal: Pancreatitis; **Central Nervous System:** Paresthesias, hallucinations, dream abnormalities, pseudotumor cerebri; **Dermatologic:** Toxic epidermal necrolysis, photoallergic skin reactions; **Special Senses:** Conjunctivitis, diplopia, optic neuritis; **Hematologic:** Bleeding episodes (e.g., epistaxis, menorrhagia); **Metabolic/Endocrine:** Gynecomastia, hypoglycemic reaction; **Cardiovascular:** Arrhythmias (sinus tachycardia, sinus bradycardia); **Allergic:** Serum sickness, lupus erythematosus syndrome, Henoch-Schönlein vasculitis; **Renal:** Renal papillary necrosis.

Reactions occurring in 3% to 9% of patients treated with *Motrin*. (Those reactions occurring in less than 3% of the patients are unmarked.)

Reactions are classified under *"Probable Causal Relationship (PCR)"* if there has been one positive rechallenge or if three or more cases occur which might be causally related. Reactions are classified under *"Causal Relationship Unknown"* if seven or more events have been reported but the criteria for PCR have not been met.

Overdosage: In cases of acute overdosage, the stomach should be emptied. The drug is acidic and excreted in the urine so alkaline diuresis may be beneficial.

Dosage and Administration: Rheumatoid arthritis and osteoarthritis. Suggested dosage is 300, 400, or 600 mg t.i.d. or q.i.d. Do not exceed 2400 mg per day. Mild to moderate pain: 400 mg every 4 to 6 hours as necessary.

Caution: Federal law prohibits dispensing without prescription.

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MED B-7-S

J-3253 June 1983

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(Continued from Page 761)

SPORTS MEDICINE

July 28-August 1—**Marine and Aquatic Sports Medicine.** UCD at Monterey. Sunday-Thursday.

SURGERY

June 17-21—**Basic Microsurgery Training Workshop.** UCSD at San Diego. Monday-Friday. 34 hrs. Fee: $1,200.

June 17-21—**Symposium on the Temporamandibular Joint.** UCSF at Maui Marriott Hotel, Maui, Hawaii. Monday-Friday. Fee: $425.

June 19-22—**Superficial Anatomy and Cutaneous Surgery.** UC, San Diego. Wednesday-Saturday. Fee: $250-$600.

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June 17-22—**The UCI Family Practice Refresher Course.** UCI at Westin South Coast Plaza, Long Beach. Monday-Saturday. 58 hrs.

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June 29-30—**7th Annual Symposium on Toxicological Emergencies.** UCSF at Cathedral Hill Hotel, San Francisco. Saturday-Sunday. Fee: $210.

June 29-July 6—**Seminar in Travel Medicine.** International Conferences at Hawaii. Saturday-Saturday. 20 hrs. Contact: International Conferences, 189 Lodge Ave., Huntington Station, NY 11746. (516) 549-0869.

June 30—**Personality and Disease: The Emerging Field of Psychoneuro-immunology.** UCSD at University of California, Santa Barbara. Sunday. 6 hrs.

July 5-7—**6th Annual Symposium: Laboratory & Clinical Aspects of Microbiological Diagnosis.** UCLA at Hotel Del Coronado, Coronado. Friday-Sunday. Fee: $175.

July 6-11—**The Fourth International Symposium on Psoriasis.** Psoriasis Research Institute at Stanford University, Stanford. Saturday-Thursday. Contact: Paul H. Jacobs, MD, Dept. of Dermatology, Stanford University Medical Center, Stanford, CA 94305.

July 8-11—**Family Practice Board Review Course.** UCSF. Monday-Thursday.

August 6-8—**Dermatopharmacology Symposium.** Stanford at Stanford. Tuesday-Thursday.

August 17-23—**Fine Needle Aspiration.** UCSF at Marriott Biltmore, Santa Barbara. Saturday-Friday. Fee: $525.

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July 24-27—**Idaho Medical Association Annual Meeting.** Sun Valley. Wednesday-Saturday. Contact: IMA, PO Box 2668, Boise 83701. (208) 344-7888.

August 3-9—**Selected Topics in Wilderness and Environmental Medicine.** Mt. Bike Tour, McCall, Idaho. Saturday-Friday. 24 hrs. Cat. I. Sponsors: University of Arizona College of Medicine and Epic Medical Expeditions. Contact: Richard Paris, MD, PO Box 209, Sun Valley 83353. (208) 788-4995.

August 15-17—**Sun Valley Emergency Medical Conference.** Sun Valley. Thursday-Saturday. Followed by a float trip on the Middle Fork of the Salmon River, August 18-20. Sponsors: Idaho Emergency Medical Services System; Idaho Chap, American College of Emergency Physicians; Idaho Chap, Emergency Nurses Assn; Idaho Committee on Trauma, American College of Surgeons; Rural Area Model System. Contact: Idaho EMS System, 450 W State St., Boise 83720. (208) 334-4245.

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(Continued on Page 874)

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WARNING

This drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual. If this combination represents the dosage so determined, its use may be more convenient in patient management. Treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

Contraindications: Concomitant use with other potassium-sparing agents such as spironolactone or amiloride. Further use in anuria, progressive renal or hepatic dysfunction, hyperkalemia. Pre-existing elevated serum potassium. Hypersensitivity to either component or other sulfonamide-derived drugs.

Warnings: Do not use potassium supplements, dietary or otherwise, unless hypokalemia develops or dietary intake of potassium is markedly impaired. If supplementary potassium is needed, potassium tablets should not be used. Hyperkalemia can occur, and has been associated with cardiac irregularities. It is more likely in the severely ill, with urine volume less than one liter/day, the elderly and diabetics with suspected or confirmed renal insufficiency. Periodically, serum K^+ levels should be determined. If hyperkalemia develops, substitute a thiazide alone, restrict K^+ intake. **Associated widened QRS complex or arrhythmia requires prompt additional therapy.** Thiazides cross the placental barrier and appear in cord blood. Use in pregnancy requires weighing anticipated benefits against possible hazards, including fetal or neonatal jaundice, thrombocytopenia, other adverse reactions seen in adults. Thiazides appear and triamterene may appear in breast milk. If their use is essential, the patient should stop nursing. Adequate information on use in children is not available. Sensitivity reactions may occur in patients with or without a history of allergy or bronchial asthma. Possible exacerbation or activation of systemic lupus erythematosus has been reported with thiazide diuretics.

Precautions: The bioavailability of the hydrochlorothiazide component of 'Dyazide' is about 50% of the bioavailability of the single entity. Theoretically, a patient transferred from the single entities of Dyrenium (triamterene, SK&F CO.) and hydrochlorothiazide may show an increase in blood pressure or fluid retention. Similarly, it is also possible that the lesser hydrochlorothiazide bioavailability could lead to increased serum potassium levels. However, extensive clinical experience with 'Dyazide' suggests that these conditions have not been commonly observed in clinical practice. Do periodic serum electrolyte determinations (particularly important in patients vomiting excessively or receiving parenteral fluids, and during concurrent use with amphotericin B or corticosteroids or corticotropin [ACTH]). Periodic BUN and serum creatinine determinations should be made, especially in the elderly, diabetics or those with suspected or confirmed renal insufficiency. Cumulative effects of the drug may develop in patients with impaired renal function. Thiazides should be used with caution in patients with impaired hepatic function. They can precipitate coma in patients with severe liver disease. Observe regularly for possible blood dyscrasias, liver damage, other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving triamterene, and leukopenia, thrombocytopenia, agranulocytosis, and aplastic and hemolytic anemia have been reported with thiazides. Thiazides may cause manifestation of latent diabetes mellitus. The effects of oral anticoagulants may be decreased when used concurrently with hydrochlorothiazide; dosage adjustments may be necessary. Clinically insignificant reductions in arterial responsiveness to norepinephrine have been reported. Thiazides have also been shown to increase the paralyzing effect of nondepolarizing muscle relaxants such as tubocurarine. Triamterene is a weak folic acid antagonist. Do periodic blood studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in post-sympathectomy patients. Use cautiously in surgical patients. Triamterene has been found in renal stones in association with the other usual calculus components. Therefore, 'Dyazide' should be used with caution in patients with histories of stone formation. A few occurrences of acute renal failure have been reported in patients on 'Dyazide' when treated with indomethacin. Therefore, caution is advised in administering nonsteroidal anti-inflammatory agents with 'Dyazide'. The following may occur: transient elevated BUN or creatinine or both, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), hyperuricemia and gout, digitalis intoxication (in hypokalemia), decreasing alkali reserve with possible metabolic acidosis. 'Dyazide' interferes with fluorescent measurement of quinidine. Hypokalemia is uncommon with 'Dyazide', but should it develop, corrective measures should be taken such as potassium supplementation or increased dietary intake of potassium-rich foods. Corrective measures should be instituted cautiously and serum potassium levels determined. Discontinue corrective measures and 'Dyazide' should laboratory values reveal elevated serum potassium. Chloride deficit may occur as well as dilutional hyponatremia. Concurrent use with chlorpropamide may increase the risk of severe hyponatremia. Serum PBI levels may decrease without signs of thyroid disturbance. Calcium excretion is decreased by thiazides. 'Dyazide' should be withdrawn before conducting tests for parathyroid function.

Thiazides may add to or potentiate the action of other antihypertensive drugs.

Diuretics reduce renal clearance of lithium and increase the risk of lithium toxicity.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis, rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting, diarrhea, constipation, other gastrointestinal disturbances; postural hypotension (may be aggravated by alcohol, barbiturates, or narcotics). Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and respiratory distress including pneumonitis and pulmonary edema, transient blurred vision, sialadenitis, and vertigo have occurred with thiazides alone. Triamterene has been found in renal stones in association with other usual calculus components. Rare incidents of acute interstitial nephritis have been reported. Impotence has been reported in a few patients on 'Dyazide', although a causal relationship has not been established.

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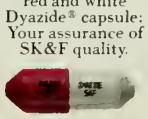

Long-term Follow-up of Patients Having Cardiac Catheterization and Cardiac Operation

Small Community Hospital Results Before and After Surgery Program

RICHARD J. FRINK, MD, *Sacramento, California;* BRUCE A. MERRICK, PhD, *Omaha;*
MARK HAMBLY, MD, *Torrance, California, and* JAMES P. ROSE, *Sacramento, California*

We followed, for a mean period of 67 months, 710 unselected consecutive cases of cardiac catheterization. Catheterizations were done on 298 patients without an in-house cardiac surgery team. When a cardiac operation was required, patients in this group were referred to a distant university medical center and were followed up after 49 and again at 103 months. After the community hospital's surgical team was established, 412 patients were catheterized and follow-up carried out for 45 months. Results show that patients in a community hospital without an in-house cardiac surgery team can be catheterized with low risk, then transferred safely to a distant center for surgical treatment without interim mortality and with good long-term results.

(Frink RJ, Merrick BA, Hambly M, et al: Long-term follow-up of patients having cardiac catheterization and cardiac operation—Small community hospital results before and after surgery program [Clinical Investigation]. West J Med 1985 Jun; 142:773-776)

We report the results of a ten-year follow-up of 710 patients having cardiac catheterizations in a small community hospital and a subsequent cardiac operation before and after establishment of an in-house cardiac surgery team. The purpose was twofold: first, to examine the risk of catheterization in a community hospital and, in addition, the risk of transfer to a distant medical center for those requiring surgical treatment; second, to compare the surgical results in a community hospital with those in a university hospital.

The risks of cardiac catheterization and the results of a cardiac operation, particularly the efficacy of coronary artery bypass procedures at the community hospital level, provide important information for hospitals considering adding cardiac surgery teams and for health planners regulating the expansion of health services. Although there are reports from cardiac surgery teams in community hospitals,[1-4] only one[3] is of long-term follow-up. There are no reports, to our knowledge, of long-term follow-up of an entire catheterization series, in which patients had or did not have an operation, by one or a group of cardiologists working in a community hospital before and after the establishment of a cardiac surgery program.

Patients and Methods

The study includes 710 unselected consecutive cardiac catheterizations done on patients referred to one cardiologist, (R.J.F.) at Mercy Hospital of Sacramento, Sacramento, California, between August 1, 1971, and January 8, 1980. Mercy Hospital, a small non-university-affiliated community hospital with 350 beds, established a cardiac catheterization laboratory in 1965 and a cardiac surgery program in October 1974. All patients were observed for at least 12 months. Follow-up was by personal interview, telephone or letter, with two separate groups evaluated.

Group A consisted of 298 patients catheterized between August 1, 1971, and October 1, 1974. These patients were followed up in 1977 after a mean interval of 49 months and again in 1981 after a mean interval of 103 months. Patients in this group who required a cardiac operation were referred to a university medical center 125 miles away. None of these

From the Department of Cardiovascular Services, Mercy Hospital of Sacramento, and the Sacramento Heart Research Foundation, Sacramento, California.
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Reprint requests to Richard J. Frink, MD, Heart Research Foundation of Sacramento, 3900 J Street, Sacramento, CA 95819.

patients required repeat catheterizations, nor were any refused surgical treatment at the university center. Group B comprised 412 patients catheterized between October 1, 1974, and January 8, 1980. The mean follow-up interval for group B was 45 months, with cardiac operations done at Mercy Hospital. The mean follow-up interval between catheterization and surgical treatment in group A was 33 days; in group B, 14 days. The groups included 495 men (70%), their ages ranging from 17 to 77 years, and 215 women, ranging in age from 20 to 82 years. The survival rate was determined by Cutler's life table method.[5]

Statistical comparisons between group A and group B were based on the χ^2 method corrected for continuity. In situations where the number of patients evaluated was fewer than 40 and the smallest expected frequency was less than 5, the Fisher exact probability test for comparing two independent variables was used.[6] Operative deaths were those occurring within 30 days after an operation. The 222 cardiac surgical procedures in group B represent 16% of all cardiac operations done at Mercy Hospital between October 1, 1974, and January 8, 1980. The remaining 84% of operations (not included in this study) were done on patients referred to the surgical team by other cardiologists. No patients were referred elsewhere for catheterization.

Indications for Catheterization and Selecting Patients for an Operation

Cardiac catheterization was done for suspected coronary disease; valvular or congenital heart disease, or a diagnosis of cardiomyopathy, pericardial constriction, hypertrophic subaortic stenosis and the like.

Patients were selected on the basis of clinical history, physical examination, a review of risk factors, results of medical treatment, all laboratory work, including the electrocardiogram, treadmill exercise test (if done) and a review of catheterization data, including coronary angiograms. Patients with valvular heart disease were selected for an operation primarily on the basis of hemodynamic findings at catheterization. In arriving at a decision for or against surgical treatment of patients with coronary atherosclerosis, strong emphasis was placed on the description and progressive nature of chest pain and the extent of coronary disease.

Chest pain was classified as stable or unstable angina pectoris on the basis of a patient's clinical history, using the following definitions: *chronic stable angina* is chronic, disabling chest pain consistent with angina pectoris, precipitated by exertion, relieved by rest or taking nitroglycerin (or both) and present for at least six months. Patients with *unstable angina pectoris* were divided into two subgroups according to the character and severity of their pain, plus electrocardiographic changes. *Unstable angina, mild,* is progressive exertional chest pain consistent with angina pectoris, with the onset between two and six months after catheterization, and unstable meaning that the pains come more frequently, are more severe, last longer and are precipitated by less and less exertion. Patients with a changing pain pattern superimposed on a previously stable condition were also included in this category. *Unstable angina, severe,* is exertional chest pain of onset within two months or less after catheterization, with a pronounced and rapid increase in frequency, severity and duration and with pains beginning to appear at rest or causing the patient to awaken from sleep. Included in this category were patients with documented transitory ST-T changes associated with the chest pain.

Angiographic Evaluation of Coronary Arteries

A scoring system, similar to that of Humphries and coworkers,[7] for each of the four major coronary arteries (main left, left anterior descending, circumflex and right) was instituted as follows:

No arteriographic abnormality	0
Narrowing of 0% to 25%	1
Narrowing of 26% to 50%	2
Narrowing of 51% to 75%	3
Narrowing of 76% to 99%	4
Complete occlusion	5

The scoring was applied only to the single greatest area of narrowing in each artery; no extra weight was given to multiple areas of narrowing in the same artery and no weight to narrowing of diagonal or secondary branches. A total score of 5 or less for all four segments was considered equivalent to single-vessel disease, a score of 6 to 10 double-vessel and a score greater than 10 was considered triple-vessel disease. Angiograms were reviewed and evaluated by a single viewer (R.J.F.).

Results

Demographic data for group A and group B are given in Table 1. The two groups are comparable and not significantly different statistically in terms of sex distribution, extent of coronary atherosclerosis, frequency of main left artery disease, normal angiograms and stable angina pectoris. Group B patients, slightly older than those in group A, had a significantly greater incidence of severe unstable angina ($P < .001$) and significantly fewer patients had mild unstable angina ($P < .001$) than did those in group A.

Table 2 includes the entire catheterization series, with medical and surgical subgroups, showing catheterization

TABLE 1.—*Demographic Data for Patients Having Cardiac Catheterization Between 8/1/71 and 10/1/74 (Group A) and Those Having Catheterization Between 10/1/74 and 1/8/80 (Group B)*

	Group A		Group B	
	No.	%	No.	%
Number of catheterizations	298		412	
Sex				
Men	210	70	285	69
Women	88	30	127	31
Mean age (years)				
Men	53		55	
Women	52		56	
One-vessel disease	57	19	71	17
Two-vessel disease	74	25	111	27
Three-vessel disease	89	30	131	32
Main left artery disease	15	5	29	7
Normal angiograms	42	14	70	17
Stable angina	53	18	98	24*
Unstable angina—mild	120	40	101	25†
Unstable angina—severe	84	28	171	42†

*$P = < .01$
†$P = < .001$

mortality, operative mortality, deaths in each group and calculated survival rates in each subgroup. The 62 patients lost to follow-up could not be traced and their status is unknown.

Most patients, 70% in group A and 71% in group B, had some form of arteriosclerotic heart disease. Coronary artery bypass operation and coronary artery bypass plus other surgical procedures constituted 82% in group A and 84% in group B of all operations done. The catheterization mortality rate, 0.1%, confirms the low risk of catheterization in a community hospital, with or without a surgical team.[8] There was no statistically significant difference between the two groups in number of patients lost to follow-up or in proportion of patients receiving medical rather than surgical therapy. The proportion of patients in each subgroup was also similar, showing no statistically significant difference between groups A and B. Survival rates at 49 months in group A were statistically not significantly different from those in group B at 45 months in the medical or surgical groups, nor in any of the subgroups.

The two groups, therefore, even though a consecutive series, are comparable not only demographically but also in the form of treatment rendered. The operative mortality rate, significantly higher in group B ($P < .01$), was due primarily to a relatively large number of deaths in the patients having coronary artery bypass plus other operations. However, when the operative mortality rates in group A and group B patients in the subgroup having coronary artery bypass only and that having coronary artery bypass plus other procedures are compared, there is no statistically significant difference ($P > .05$ in both instances). It should be noted that the number of patients is relatively small in both of these subgroups, with the few deaths making valid statistical comparisons difficult. Of five operative deaths in the coronary-artery-bypass-procedure subgroup, two occurred in patients with severe unstable angina. No deaths in group A and two deaths in group B patients occurred between catheterization and surgical treatment. One patient suffered an acute myocardial infarction between catheterization and operation. Of a total of 394 surgical cases, 380 (96%) were contacted for follow-up. Of the 14 surgical cases lost to follow-up, 11 were for coronary artery bypass procedure only.

Discussion

Community hospitals play a vital role in the health care of most Americans. The incidence of heart disease, the most common health problem, requires that all hospitals provide adequate facilities for the care of these patients. It is natural that community hospitals should endeavor to provide all reasonable services possible in or near a patient's home environment.[3,4] The growth and increasing sophistication of cardiac care in the private hospital sector, including cardiac operations, reflect the mounting demand for such services and the availability of adequately equipped and trained professional personnel. Initial surgical results reported from com-

TABLE 2.—*Comparison of Operative Mortality Rates and Long-term Results: Group A at 49 and 103 Months, Group B at 45 Months, With Follow-up of Entire Group at 67 Months*

	Group A 49 mo.		Group B 45 mo.		Group A 103 mo.		Groups A & B 67 mo.	
Procedures	*No.*	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*
Number of catheterizations	298		412		298		710	
Number contacted for follow-up	271	91	385	93	263	88	648	91
Catheterization mortality	0	0	1	0.2	0	0	1	0.1
Cardiac surgery—all cases	172	58	222	54	172	58	394	55
Deaths—operative (30 days)	0	0	11	5*	0	0	11	3
Survival		89		86		79		83
CAB procedure only	128	43	159	39	128	43	287	40
Deaths—operative (30 days)	0	0	5	3†	0	0	5	2
Survival		93		93		85		89
CAB plus other‡	13	4	28	7	13	4	41	6
Deaths—operative (30 days)	0	0	6	21§	0	0	6	15
Survival		46		61		46		56
Valvular and/or other‡	31	10	35	8	31	10	66	9
Deaths—operative (30 days)	0	0	0	0	0	0	0	0
Survival		80		74		67		71
Medical treatment—all cases	126	42	190	46	126	42	316	45
Survival		90		93		88		91
Coronary atherosclerosis	67	22	107	26	67	22	174	25
Survival		90		93		85		90
Valvular and/or miscellaneous‖	17	6	13	3	17	6	30	4
Survival		82		84		81		82
Normal arteriograms	42	14	70	17	42	14	112	16
Survival		95		94		92		93
Deaths, all cases	33	11	44	11	50	17	94	13
Survival		88		89		82		86

CAB=coronary artery bypass

*$P < .01$.
†$P > .1$.
‡Other includes ventricular aneurysm resection or valve replacement (or both).
§$P > .05$.
‖Miscellaneous includes congenital heart disease, hypertrophic cardiomyopathy, pericardial constriction, primary cardiomyopathy and mitral valve prolapse.

munity hospitals have been encouraging and comparable to those in large medical centers.[1-4] By 1980, the number of cardiac surgery teams had expanded so that less than 25% of coronary artery bypass procedures were being done in university or federal hospitals. Most bypass operations were being done by surgeons in the private sector engaged in single-specialty group practice.[9]

Federal and state regulations frequently require a certificate of need before a cardiac catheterization laboratory can be established in a community hospital. Many states do not allow a catheterization laboratory without an in-house cardiac surgery team. The difficulties in establishing, at the same time, both a catheterization laboratory and a surgical team, along with meeting the requirement for a minimum number of cases per year, are very great. Such regulations were designed to decrease health care costs by preventing duplication of equipment, to improve efficiency through economy in numbers and to increase a program's success through adequate surgical experience.[10] However, studies show no decrease in costs associated with an increased number of cases,[11] no increased risk for catheterizations carried out in community hospitals without a cardiac surgery program[12] and, although surgical mortality rates decreased with an increased number of procedures.[10] volume of cases is not per se a guarantee of quality.[13] McGregor and Pelletier[14] pointed out that cardiac surgery costs are high for fewer than 50 surgical cases per year, but they noted that no studies related outcome to turnover, nor do they consider cost to families.

Our study shows that cardiac catheterization can be done safely in a community hospital where there is no in-house cardiac surgery team, and that patients can be transferred safely to a distant medical center if a surgical procedure is required. An in-house cardiac surgery team can be established when the volume of catheterization and surgical cases warrants. Restrictions on the expansion of cardiac facilities, particularly on the establishment of a cardiac catheterization laboratory, may not be in the best interests of patients, may not be cost-effective[3,4,11] and may actually lower or restrict the delivery of high-quality care in community hospitals. Catheterization laboratories, properly equipped and staffed with rigid quality control, are a valid addition to many hospitals.[12]

Cardiac Surgery Results and Community Hospitals

Do the results of cardiac surgery—both short and long term—in a community hospital justify the expenditure of time, personnel and resources necessary to establish a cardiac surgery team? Assuming local medical care is more cost-effective than distant referral care, can patients and attending physicians expect comparable surgical results in a community hospital?

Because coronary atherosclerosis was the predominant cardiac problem in this study, the surgical results in patients with coronary atherosclerosis are emphasized. The two groups studied are exceptionally well matched in all variables except in the frequency of severe unstable angina, which increased after a surgical team was established. The reasons for this are not clear, but they may reflect an increasing awareness by referring physicians of the possible benefits of a coronary artery bypass operation. The presence of a surgical team also tends to increase the number of referrals of cardiac patients previously sent directly to a distant center having a surgical team. Group B patients may, therefore, be considered at slightly greater risk for a sudden cardiac event than group A. Nevertheless, the similarity of the two groups provides an opportunity to compare results of treatment in a community hospital with those in the university center.

Table 2 shows the surgical results to be comparable, except in the area of operative mortality. The operative (30-day) mortality rate was significantly higher statistically in group B patients ($P < .01$). Possible reasons for this include a higher percentage of patients with unstable angina, a relatively high mortality rate in patients requiring coronary artery bypass plus other surgical treatment, the experience of the surgical team and a zero operative mortality in group A. A zero operative mortality rate is unusual and is attributed to the skill and sophistication of the university surgical team.

This record was not matched in the community hospital, even though surgical techniques improved and operating deaths decreased. Statistically, however, when one looks at the specific subgroups—coronary artery bypass operation alone or coronary artery bypass plus other operations—there is no significant difference in operative mortality ($P > .05$ in both instances).

The general trend in the data suggests operative mortality to be higher in group B. However, when the group B results are compared with those of other community hospitals or other large university hospitals, the results are comparable.[3,15] Because of the relatively large number of deaths in the subgroup having coronary artery bypass plus other surgical procedures, it may be judicious, especially in the initial phase of a new cardiac surgery program, to consider referring complicated cases to a more established surgical team.

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American Visceral Leishmaniasis (Kala-azar)

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Visceral leishmaniasis (kala-azar) is an important cause of morbidity and mortality in widely scattered areas of the world. To better characterize the South American form of the disease, the clinical and laboratory manifestations of 29 patients admitted to hospital (18 male and 11 female patients, mean age 4.9 years), were assessed in an endemic area in northeastern Brazil. Fever, weight loss, pronounced splenomegaly, hepatomegaly, anemia, thrombocytopenia, relative neutropenia, hypoalbuminemia and hypergammaglobulinemia were found in the majority of patients. Symptoms were often present for two or more months before diagnosis. Secondary infections complicated many cases; there were ten cases of pneumonia and half of the patients had one or more intestinal parasites. The average length of hospital stay was 27 days; all patients were treated with meglumine antimoniate (Glucantime). The mortality rate was 3%. American visceral leishmaniasis remains an important disease among children living in endemic areas.

(Evans T, Reis MFFE, de Alencar JE, et al: American visceral leishmaniasis (kala-azar). West J Med 1985 Jun; 142:777-781)

Visceral leishmaniasis (kala-azar), caused by the protozoal parasite *Leishmania donovani,* is an important cause of morbidity and mortality in many areas of the world.[1,2] Not widely appreciated by physicians in North America is that visceral leishmaniasis is primarily a disease of children and young adults in Brazil and other areas of South America. It also primarily affects children in the Mediterranean littoral. In India and Africa it is more common among adults, but also occurs in children. The threat of leishmaniasis, both visceral and the various cutaneous syndromes, is severe enough that the World Health Organization has identified it as one of the six major parasitic diseases for study in the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases.

L donovani is a dimorphic protozoan. It exists without an exteriorized flagellum as an intracellular amastigote within mammalian mononuclear phagocytes and as a flagellated, extracellular promastigote in its arthropod vector, the sand fly. In the Americas and the Mediterranean littoral, the disease is a zoonosis involving domestic dogs. In Brazil, foxes serve as a wild reservoir as well. *L donovani* is transmitted to humans by the bite of an infected sand fly. Although *L donovani* is not endemic in the United States, it poses a risk to travelers living in endemic areas and to immigrants to North America from those areas. This study was designed to assess the clinical manifestations and course of American visceral leishmaniasis among children in northeastern Brazil.

Patients and Methods

The charts of all patients with a discharge or autopsy diagnosis of American visceral leishmaniasis admitted to the pediatric ward of the Hospital das Clinicas, Universidade Federal do Ceará, Fortaleza, Ceará, Brazil, from January through December 1982 were reviewed. The ward admits only patients younger than 16 years. Charts were identified by records kept and sent to the Campanha Contra a Leishmaniose as required by law. Histories, physicals and daily notes were kept by pediatric residents or senior medical students supervised by the residents. A standardized admission form was used, and standard laboratory studies were done in all cases of possible visceral leishmaniasis.

A total of 31 cases was identified. Of these, two were

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TABLE 1.—*Presenting Complaints in Patients With American Visceral Leishmaniasis*

Symptom	Patients With Symptom*	
	Number	Percent
Fever	19	66
Abdominal pain or enlargement	15	52
Pallor	4	14
Weight loss	2	7
Edema	1	3
Jaundice	1	3

*Data from 29 patients: some had more than one presenting symptom.

excluded from this study, one a patient in whom an autopsy showed acute lymphocytic leukemia and no evidence of visceral leishmaniasis, and another a patient who was referred for evaluation of antimony toxicity after therapy for visceral leishmaniasis had been completed. A diagnosis of American visceral leishmaniasis was established by identifying *Leishmania* species amastigotes in either bone marrow aspirate or a hepatic biopsy specimen (one case); an indirect immunofluorescent antibody titer of 1 to 80 or greater with a consistent clinical picture, or a clinical presentation that consisted of at least five of the following six criteria: fever, weight loss, hepatosplenomegaly, pancytopenia, nondiagnostic bone marrow aspirate for other disease processes and a negative Widal reaction. Although the antileishmanial immunofluorescent antibody test can be positive in cases of Chagas' disease, schistosomiasis or other infections, it was positive in only 11 of 156 residents (7%) from this area who did not have an illness with the features of American visceral leishmaniasis (L. H. Harrison, MD, T. G. Naidu, PhD, R. D. Pearson, MD, et al, unpublished data, March 1982).

Records were examined and the following data were systematically recorded: age, sex, residence, presenting symptoms, duration of illness, chief complaint(s) and whether the patient had fever, anemia or pallor, abdominal enlargement, lethargy, weight loss, anorexia, hemorrhagic tendencies (epistaxis, hematuria, ecchymosis), documented parasitic infections, edema or jaundice. A variety of laboratory data were recorded in relation to the treatment protocol. In general, treatment consisted of a 10- to 13-day course of daily injections of meglumine antimoniate (Glucantime), approximately 20 mg of pentavalent antimony per kg per day, followed by a treatment-free interval of 10 to 20 days and then another course of injections of meglumine antimoniate daily for 10 to 13 days. Data gathered before the fourth injection were considered "initial values," and data obtained within five days of the last dose or after therapy were placed in a "final values" category. All other values obtained were considered to be "during treatment." Patients were also evaluated two to four weeks after the final injection of antimony for signs of recurrent visceral leishmaniasis. The patients were arbitrarily divided by age into a group 3 years of age or younger and a group older than 3 years for comparison.

Results

In all, 29 patients, 18 male and 11 female, were admitted to the pediatric unit of the Hospital das Clinicas with American visceral leishmaniasis in 1982. The mean age was 4.9 years. The diagnosis was made in 16 cases by identifying *Leishmania* amastigotes in a bone marrow aspirate, in 1 case in a hepatic biopsy specimen, in 9 cases by clinical presentation and serology (immunofluorescent antibody titer of 1 to 80 or greater) and in 3 cases by clinical criteria alone after ex-

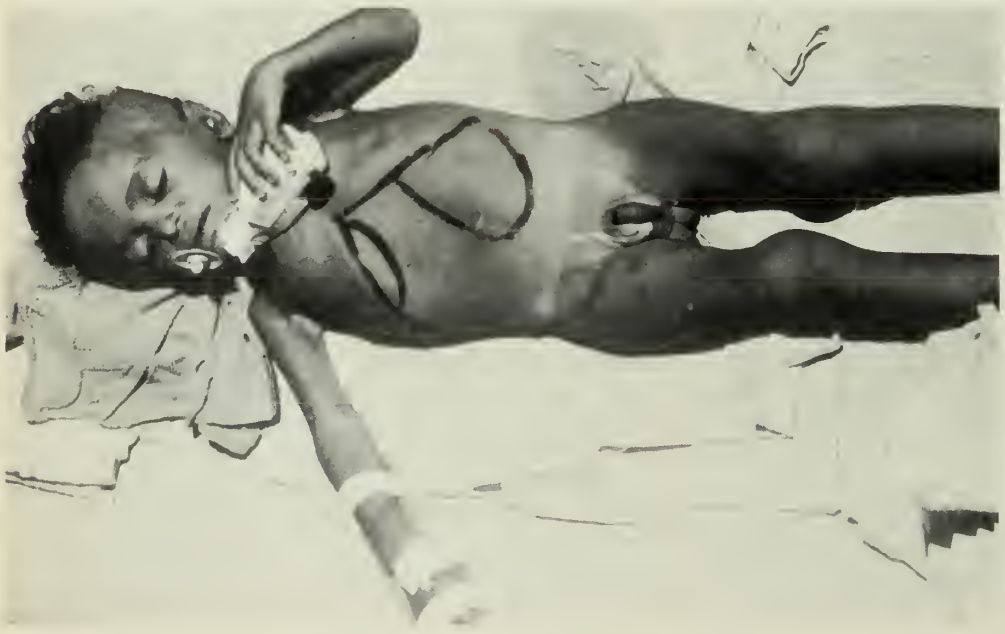

Figure 1.—Brazilian child with American visceral leishmaniasis. Note pronounced splenomegaly and hepatomegaly.

cluding other illnesses. Noteworthy was the observation that ten patients gave a history of one or more family members or neighbors who had been treated for visceral leishmaniasis.

The mean duration of symptoms before diagnosis was 3.1 months for all patients—1.9 months for patients 3 years of age or younger and 4.3 months for those older than 3 years. However, five patients had symptoms of one month or less duration and one had symptoms for only eight days. The most common of the 42 "chief complaints" recorded from the 29 patients were fever (19 patients) and abdominal enlargement or pain (15 patients) (Table 1). Other patients presented with pallor, weight loss, edema or jaundice.

All signs and symptoms encountered at the initial history and physical examination are recorded in Table 2. Fever and lethargy were universal (29); abdominal enlargement (26), weight loss (25/26 [96%]) and anorexia (23/25 [92%]) were also common. Edema, bleeding tendencies and jaundice were encountered less frequently. On examination of the abdomen there were a palpable spleen in 27 (93%) patients and hepatomegaly, defined as a liver edge greater than 2 cm below the right costal margin, in 22 (76%) cases. A typical patient with hepatosplenomegaly is seen in Figure 1. Of all patients, 25 (86%) and 17 (59%) had spleens greater than 4 cm or 7 cm below the left costal margin, respectively. In 26/28 (93%) cases the spleen was further below the left costal margin than the liver was below the right costal margin. However, precise interpretation of these measurements was limited due to the varying ages and heights and weights of the patients.

Hematologic values are presented in Table 3. At presentation, 26 (90%) patients had hematocrits of less than 30%. Later hematocrit determinations were influenced by occasional blood transfusions given to patients with critically low hematocrits. After completion of the first series of treatments, the hematocrits were higher in all but one case. In that instance there appeared to be persistent postleishmaniasis hypersplenism. All patients presented with leukocyte counts of less than 6,000 per μl; 22 (76%) were less than 4,000 per μl. After treatment only 1 of 18 patients remained leukopenic (leukocyte count less than 4,000 per μl). Patients tended to present with relative neutropenia (mean, 34% polymorphonuclear leukocytes), a relative lymphocytosis (mean, 60% lymphocytes) and eosinopenia (25[86%] patients had no eosinophils in their peripheral smear). After treatment all patients had eosinophils in their peripheral smears, and there was an increase in the polymorphonuclear leukocyte: lymphocyte ratio.

Patients on admission also tended to be thrombocytopenic (26/27 had a platelet count of less than 150,000 per μl); an increase in platelets occurred during therapy. Only 1/12 remained thrombocytopenic after treatment. Finally, the mean erythrocyte sedimentation rate in 22 patients was 91 ± 46 (standard deviation [SD]) mm of mercury per hour with 14 (64%) patients having a rate of greater than 80. After treatment, the sedimentation rate fell to 48 ± 32 mm of mercury per hour, but 2/12 patients continued to have values of greater than 80.

Examination of serum proteins showed depressed albumin levels with an elevated γ-globulin fraction in most cases (Table 4). In all, 17/27 (63%) patients presented with an albumin level of less than 2.5 grams per dl; the mean was 2.4 grams per dl. In 15/25 (60%) cases the albumin to total globulin ratio was less than or equal to 1.0.

The duration of hospital stay varied, but the average was 27 days. Some patients were discharged after completion of one course of antimony therapy at about two weeks whereas others required longer hospital stays. Secondary infections requiring antibiotic therapy complicated many of the cases. There were 10 radiologically documented cases of pneumonia among the 29 patients. In addition, 15 (52%) patients had one or more helminths or protozoa documented by stool examination at the time of admission. One patient died while in hospital, giving an overall mortality rate of 3%.

Follow-up examinations were done on 25 of the 28 surviving cases two to four weeks after completion of therapy. No patient remained febrile, two patients had no decrease in splenic enlargement, two other patients had resolving splenomegaly with persistent hepatomegaly and in all of the others both splenomegaly and hepatomegaly were greatly reduced.

Discussion

American visceral leishmaniasis in Brazilian children is characterized by fever, abdominal enlargement or pain,

TABLE 2.—*Signs and Symptoms of American Visceral Leishmaniasis*

Sign or Symptom	*Patients With Symptom/ Total Patients*	
Fever	29/29	(100)*
Lethargy	28/28	(100)
Pallor	27/28	(96)
Weight loss	25/26	(96)
Anorexia	23/25	(92)
Abdominal enlargement	26/29	(90)
Edema	9/28	(32)
Bleeding episodes	6/29	(21)
Jaundice	5/28	(18)
Spleen palpable	27/29	(93)
≥4 cm below left costal margin	25/29	(86)
≥7 cm below left costal margin	17/29	(59)
Liver ≥2 cm below right costal margin	22/29	(76)
Spleen ≥liver	26/28	(93)

*Percentage of patients is in parentheses.

weight loss, splenomegaly, hepatomegaly, anemia, thrombocytopenia, relative neutropenia, hypoalbuminemia and hypergammaglobulinemia. Symptoms are often present for several months before diagnosis, but the disease can present with a subacute course.

Although American visceral leishmaniasis occasionally develops in adolescents and young adults in Brazil, epidemiologic studies have previously shown that the disease primarily affects children. Alencar and Neves found that 61% of all cases occurred in children younger than 4 years and 81% occurred in patients younger than 10 years.[1]

The clinical manifestations of visceral leishmaniasis in Brazil appear to be similar to those reported from the Mediterranean littoral, East Africa, India and China, though the age of the patients varies from one location to another.[1] As noted by other authors, an immense spleen, often found below the level of the umbilicus, is an important indication of American visceral leishmaniasis. In other diseases associated with splenomegaly, such as schistosomiasis mansoni, amebic liver abscess and acute lymphocytic leukemia, there is often a relatively more substantial degree of hepatomegaly. Rarely does the spleen during Chagas' disease, miliary tuberculosis, brucellosis or typhoid fever reach the pronounced proportion of that observed in many patients with visceral leishmaniasis.

Pancytopenia during visceral leishmaniasis was also observed in our patients. The majority presented with hematocrits less than 30%, leukocyte counts less than 4,000 per μl and platelets less than 100,000 per μl. Because bone marrow was aspirated in every case, acute leukemia was quickly excluded. The anemia of American visceral leishmaniasis is thought to be due to a combination of factors including intravascular hemolysis, marrow replacement with *Leishmania*-infected mononuclear phagocytes, hemorrhage or splenic sequestration of erythrocytes.[3,4] Complement has previously been found on erythrocytes in patients with visceral leishmaniasis.[4] It is not known whether the observed neutropenia is due to increased margination or splenic sequestration of polymorphonuclear leukocytes, an autoimmune process, decreased marrow production or a combination of these factors.[5] Eosinopenia may be a helpful diagnostic sign as it was common among our patients before treatment, with 25 patients having no eosinophils identified in their peripheral smears. After therapy, all patients had eosinophils. The sedimentation rate was elevated in most cases and remained so, but to a lesser degree, throughout and following treatment. Circulating immune complexes and rheumatoid factors are also prevalent among patients with visceral leishmaniasis.[2]

In an endemic area or in a traveler or emigrant from such an area, the constellation of prolonged fever, progressive weight loss, weakness, pronounced splenomegaly, hepatomegaly, anemia, leukopenia, hyperglobulinemia and hypoalbuminemia are highly suggestive of visceral leishmaniasis. A definitive diagnosis depends on finding amastigotes in tissue or isolating the organism in culture. Bone marrow aspiration is probably the safest diagnostic procedure; amastigotes are seen on Wright-Giemsa-stained smears in about half to two thirds of cases.[6] Splenic puncture (98% positivity)[7] is a more sensitive diagnostic method and is routinely done in East Africa. It can be associated with serious hemorrhage, particularly in patients with advanced stages of disease who have an associated coagulopathy, but the morbidity and potential mortality appear to be less when aspiration is done quickly through a small-bore needle in patients with no laboratory evidence of coagulopathy.[7] A liver biopsy specimen is less likely to yield the diagnosis than splenic puncture, and it too carries the risk of life-threatening hemorrhage.

Although not carried out in this study, culture of bone marrow, liver, spleen or other tissues may show the parasite. Specimens can be inoculated into Novy, MacNeal and Nicolle's medium or one of several media that do not contain blood such as Schneider's insect medium[8] and maintained at 22°C to 26°C. Motile promastigotes develop from amastigotes and multiply. They can be identified in positive cultures in a few days to several weeks. Culture of *L donovani* should always be attempted in evaluating possible cases of visceral leishmaniasis in North America because the yield is greater than with histology alone.

Several tests have been developed to detect specific antileishmanial antibodies. Indirect immunofluorescent antibody tests, enzyme-linked immunoabsorbent assays and counter-

TABLE 3.—*Hematologic Values in Patients With American Visceral Leishmaniasis**

	Presentation	*During Treatment*	*Posttreatment*
Hct (%) ($\bar{x}\pm$SD)	24±6	32±9	33±6
≤20%	8/29 (28)	2/15 (13)	1/18 (6)
≤30%	26/29 (90)	6/15 (40)	4/18 (22)
Leukocyte Count (per μl) ($\bar{x}\pm$SD)	3,140±1,220	5,820±3,300	7,360±2,300
≤2,000	8/29 (28)	3/13 (23)	0/18 (0)
≤3,000	17/29 (59)	3/13 (23)	0/18 (0)
≤4,000	22/29 (76)	5/13 (38)	1/18 (6)
≤6,000	29/29 (100)	6/13 (46)	2/18 (11)
Platelets ($\times 10^{-3}$) ($\bar{x}\pm$SD)	69±47	154±85	244±79
<100	21/27 (78)	4/11 (36)	0/12 (0)
<150	26/27 (96)	5/11 (45)	1/12 (8)

Hct= hematocrit, SD=standard deviation

*The figures in the table represent the number of patients with the value versus the number tested, with the percentage in parentheses.

TABLE 4.—*Serum Protein Values in Patients With American Leishmaniasis**

	Presentation	*Posttreatment*
Total protein (grams/dl) ($\bar{x}\pm$SD)	6.9±1.1	8.0±1.2
≥7.0 grams/dl	11/27 (41)	17/21 (81)
Albumin (grams/dl) ($\bar{x}\pm$SD)	2.4±0.6	3.7±0.8
≤2.5 grams/dl	17/27 (63)	1/20 (5)
γ-Globulin (grams/dl) ($\bar{x}\pm$SD).....	2.8±1.2	2.6±0.8
≥2.0 grams/dl	17/25 (68)	10/12 (83)

SD=standard deviation

*The figures in the table represent the number of patients with the value versus the number tested, with the percentage in parentheses.

immunoelectrophoresis appear to be sensitive.[6,9] Complement-fixation, hemagglutination and direct agglutination tests also have their proponents. Unfortunately, each of these tests is to some degree dependent on the *Leishmania* species used as antigen and the method of antigen preparation. Cross-reactions associated with leprosy, Chagas' disease, malaria, schistosomiasis and cutaneous leishmaniasis may occur. However, we found a positive antileishmanial immunofluorescent antibody test (titer 1 to 80 or greater) in only 7% of 156 donors without a compatible clinical presentation in the visceral leishmaniasis endemic area near Sobral, Ceará, Brazil (L. H. Harrison, MD, T. G. Naidu, PhD, R. D. Pearson, MD, et al, unpublished data, March 1982). A positive test for antileishmanial antibody thus supports the diagnosis of visceral leishmaniasis but does not confirm it. The leishmanin skin test (Montenegro test), a test of delayed hypersensitivity to leishmanial antigen, is negative during active visceral leishmaniasis and becomes positive only after successful therapy. Although useful in studies of epidemiology, it is of no value in documenting active visceral leishmaniasis.

The follow-up period in our study was short, two weeks to one month after the last dose of meglumine antimoniate, and thus does not provide data on late relapses. The observed low in-hospital mortality (one patient) in our series may not be entirely representative as several deaths occurred in the four months immediately following the study period. It is noteworthy that secondary infections were common among our patients. There were ten cases of radiologically documented pneumonia. Intestinal parasites were likewise prevalent, as they are among children without visceral leishmaniasis living in this area. The mortality rate in an endemic area is likely to be influenced by several factors such as patient age, delay in diagnosis, nutritional status, the incidence of secondary infections and the dosage and duration of therapy. Unfortunately, no controlled studies have been done in the New World to determine the optimal dose and duration of pentavalent antimony therapy. Recent studies in East Africa indicate that pentavalent antimony compounds (20 mg of pentavalent antimony per kg of body weight per day to a maximum of 850 mg of pentavalent antimony per day) are well tolerated and that daily or twice-a-day therapy for 20 days or more without a "rest period" between treatment courses is safe.[6,10,11] Prospective studies are still needed to determine the optimal treatment regimen for American visceral leishmaniasis.

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Computed Tomography in Cases of Coccidioidal Meningitis, With Clinical Correlation

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Cranial computed tomographic (CT) scans of 22 patients with coccidioidal meningitis were reviewed and their clinical course was analyzed. Abnormalities of the ventricular system or the basilar cisterns or both were present in 16 instances. Although it is not a definitive diagnostic tool, the CT scan is helpful in suggesting a diagnosis of coccidioidal meningitis and in predicting the prognosis of patients affected by the disease.

(Shetter AG, Fischer DW, Flom RA: Computed tomography in cases of coccidioidal meningitis, with clinical correlation. West J Med 1985 Jun; 142:782-786)

Coccidioidal meningitis is a fungal infection affecting visitors to and residents of the southwestern United States. Although the disease is relatively rare, it is a source of considerable mortality and morbidity when it occurs. The initial signs and symptoms of coccidioidal meningitis are often nonspecific and may be unaccompanied by a history of systemic infection, thereby delaying early diagnosis and treatment. We undertook a retrospective analysis of cranial computed tomographic (CT) scans in patients with coccidioidal meningitis to determine whether this test is capable of providing useful information regarding diagnosis, treatment or prognosis.

Methods

Cranial CT scans of 22 patients diagnosed as having coccidioidal meningitis at the Barrow Neurological Institute from 1975 to 1981 were reviewed. Scans were done on either an upgraded EMI Mark I scanner or a Delta 2020 scanner. Contrast enhancement by drip infusion was carried out in 17 patients. All scans were interpreted by a neuroradiologist (R.A.F.) who did not know the patients' clinical status. The scans were evaluated for hypodense or hyperdense areas, the presence of hydrocephalus (generalized or compartmentalized) and cisternal integrity.

Patients with coccidioidal meningitis ranged in age from 2 to 80 years, with a mean of 39 years. There were 15 male and 7 female patients. Six patients were white, three were Mexican-American, three were American Indian, one was Filipino and one was black; in eight instances race was not specified. In all patients cerebrospinal fluid specimens showed positive coccidioidal complement fixation titers, which were reactive at 1:4 or greater. Of the 22 patients, 12 (55%) who had meningitis had no previous history of a coccidioidal infection. The neurologic state of patients at the time of their first CT scan was documented by hospital chart review. Follow-up information was obtained through a questionnaire and by review of recent charts.

All patients received amphotericin B intrathecally. Other therapeutic modalities used in selected instances included systemic amphotericin B, systemic or intrathecal isonidazole compounds and ventricular shunting. A full discussion of the diagnosis and treatment of coccidioidal meningitis is beyond the scope of this paper and has been covered elsewhere.[1-5]

Results

Of 22 patients, 6 (27%) with coccidioidal meningitis were felt to have normal CT scans at the time of initial diagnosis. Scans of the remaining patients (73%) showed single or combined abnormalities in ventricular size, basal cisterns or brain parenchyma (Table 1).

The ventricular system was enlarged in either a generalized or an asymmetric fashion in 15 of 22 patients (Table 2). Seven of these patients had diffuse ventriculomegaly affecting the lateral, third and fourth ventricles in equal degree. An example of this type of abnormality is seen in Figure 1. The remaining patients had compartmentalized hydrocephalus. Examples of asymmetric ventricular enlargement in cases of coccidioidal meningitis are shown in Figure 2.

Enhancement or obliteration, or both, of the basal cisterns was the second most common abnormality seen on CT scan and was present in 12 patients (55%). One patient had cis-

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Submitted, revised, September 17, 1984.

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TABLE 1.—*Computed Tomographic Scan Findings in 22 Patients With Coccidioidal Meningitis**

Findings	*No. of Patients*
Normal	6
Ventricular dilatation	15
Cisternal obliteration	5
Cisternal enhancement	3
Cisternal obliteration and enhancement	4
Hypodense white matter lesions	2
Ependymal enhancement	1

*Of the 16 patients who had abnormal findings on scans, some had several abnormal features (see text for more details).

TABLE 2.—*Patterns of Ventricular Dilatation in 15 Patients With Coccidioidal Meningitis*

Ventricular Dilatation	*No. of Patients*
Generalized	7
Large lateral and third ventricles plus	
Nonvisualized fourth ventricle	2
Mildly dilated fourth ventricle	2
Greatly dilated fourth ventricle	3
Asymmetric dilatation of the temporal horn	1

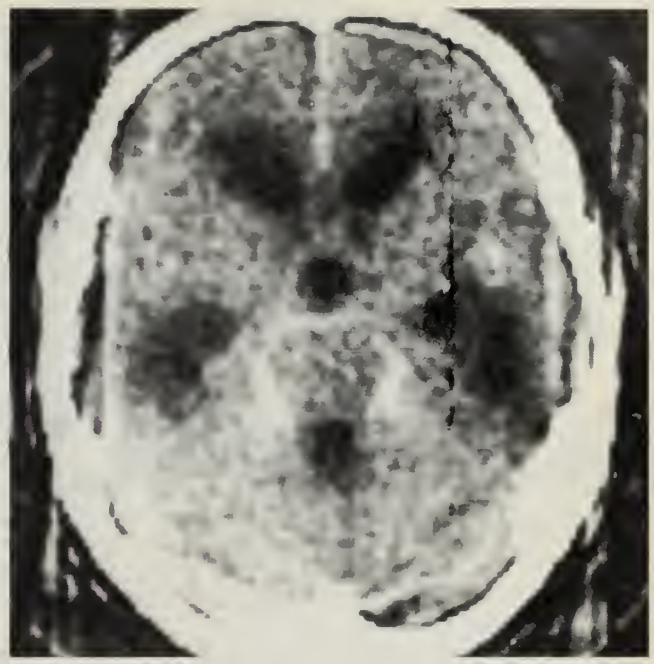

Figure 1.—Computed tomographic scan showing generalized (symmetric) dilatation of the ventricular system. Note the enhancement of the basal cisterns.

ternal involvement with normal-sized ventricles, while the remaining 11 patients had some degree of ventricular enlargement in combination with their cisternal abnormalities. Examples of cisternal abnormalities are shown in Figure 3.

One patient had ependymal enhancement and abnormalities in the cisternal region. Brain parenchymal abnormalities were seen in two patients and consisted of small hypodense areas in the subcortical white matter. There were no instances of hypodense zones within gray matter structures in our series. Hyperdense parenchymal abnormalities such as hemorrhage or calcification were also not encountered.

The clinical state of patients at the time a diagnosis of coccidioidal meningitis was established was correlated with their initial CT scan. Fourteen patients had no focal neurologic deficits but had signs and symptoms of meningeal irritation such as headache, low-grade fever and nuchal rigidity. The remaining eight patients had indications of meningeal irritation but also showed evidence of impaired mentation, personality change, depressed level of consciousness or signs of elevated intracranial pressure. Patients with abnormalities apparent on CT scans were considerably more likely to have evidence of neurologic impairment than those with normal scans. Of 16 persons with a CT scan abnormality at the time of initial diagnosis, 7 (44%) presented with lethargy, confusion or papilledema, compared with one of six patients (17%) with a normal CT scan and a similar clinical picture.

Attempts were also made to correlate long-term clinical outcome with initial CT scan findings. Follow-up data were obtained through December 1981 or up to the time of death in 18 patients. Four patients were lost to follow-up before the completion of our study. In the group with normal CT scans, a single death was recorded in an 80-year-old man who died of a myocardial infarction unrelated to his coccidioidal meningitis. The remaining five patients were alive at the time of the last follow-up and were leading independent lives (average follow-up time, 18 months). There were 5 deaths in the 16

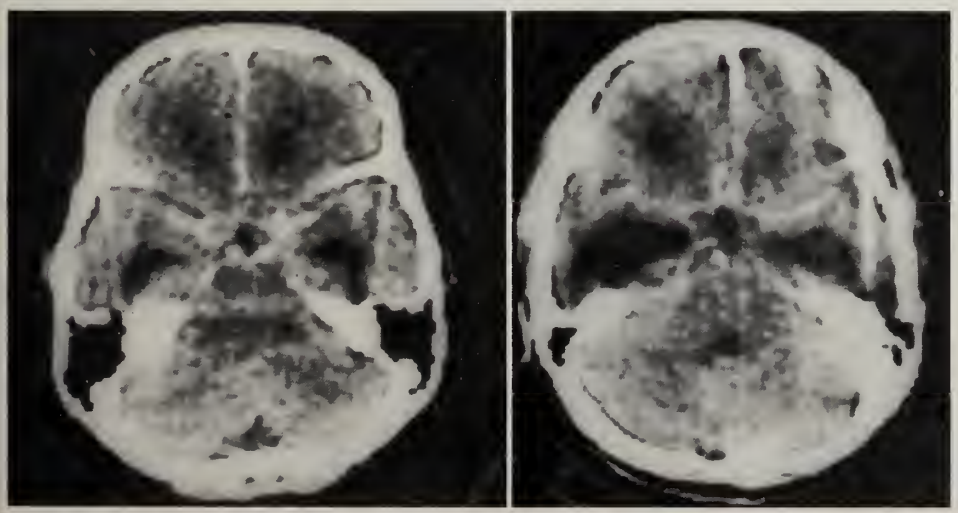

Figure 2.—Compartmentalized (asymmetric) dilatation of the ventricular system. **Left,** There is nonvisualization of the fourth ventricle, and, **Right,** a mildly dilated fourth ventricle.

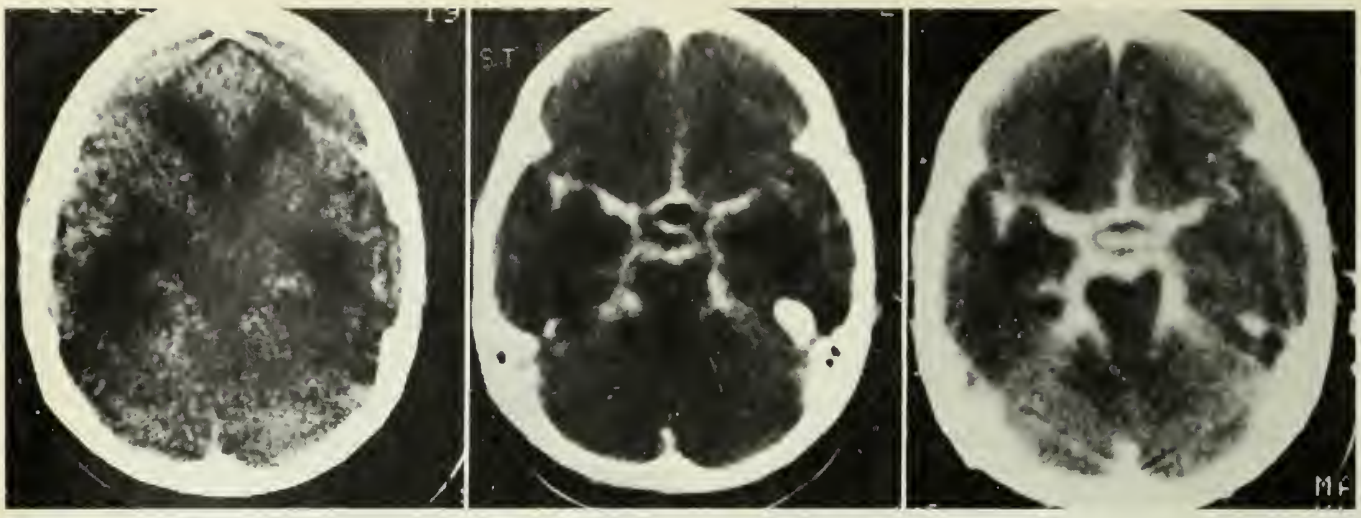

Figure 3.—Obliteration of the basal cisterns, **Left,** followed by cisternal enhancement after intravenous administration of contrast medium, **Middle. Right,** There is striking progression in the magnitude of enhancement at follow-up scan one month later.

patients whose CT scans were abnormal initially. Four patients died of complications of their disease and one patient died of an intracerebral hemorrhage that may have been unrelated to his infection. Of the remaining 11 patients, 5 were functioning independently, 3 were semidependent but resided at home and 3 were totally dependent on nursing-home care (average follow-up time, 34 months). These findings suggest that patients with coccidioidal meningitis whose initial CT scan is normal have a better long-term prognosis than those with ventricular or cisternal CT scan abnormalities at the time a diagnosis is made.

Follow-up CT scans were obtained in a number of cases and were of value in assessing progressive hydrocephalus or the response to ventricular shunting. Two patients were of particular interest in this regard. Both underwent lateral ventricular shunting for generalized ventriculomegaly and symptoms of elevated intracranial pressure. At three and six months postshunting, repeat CT scans showed pronounced enlargement of the fourth ventricle that had not been present initially (Figure 4). This was associated with clinical evidence of posterior fossa hypertension. The possibility of isolated fourth ventricular dilatation in patients with coccidioidal meningitis with lateral ventricular shunts must be kept in mind if posterior fossa symptoms develop. The appropriate diagnosis can be readily established by repeat CT scanning.

Discussion

Coccidioides immitis is a fungal organism endemic to the southwestern United States and to certain regions of Central and South America. It manifests itself most frequently as a benign and self-limited pulmonary infection. However, in less than 1%[3] of affected patients, hematogenous dissemination to the central nervous system may occur. The signs and symptoms of coccidioidal meningitis are meningeal irritation, increased intracranial pressure or impaired mentation. The cerebrospinal fluid will show a fungal or tuberculous meningitis, including nongranulocytic leukocytosis, an elevated protein value and a moderately depressed glucose level. The organism itself is rarely cultured from a spinal fluid specimen and a definitive diagnosis is established by obtaining a positive cerebrospinal fluid complement fixation titer.

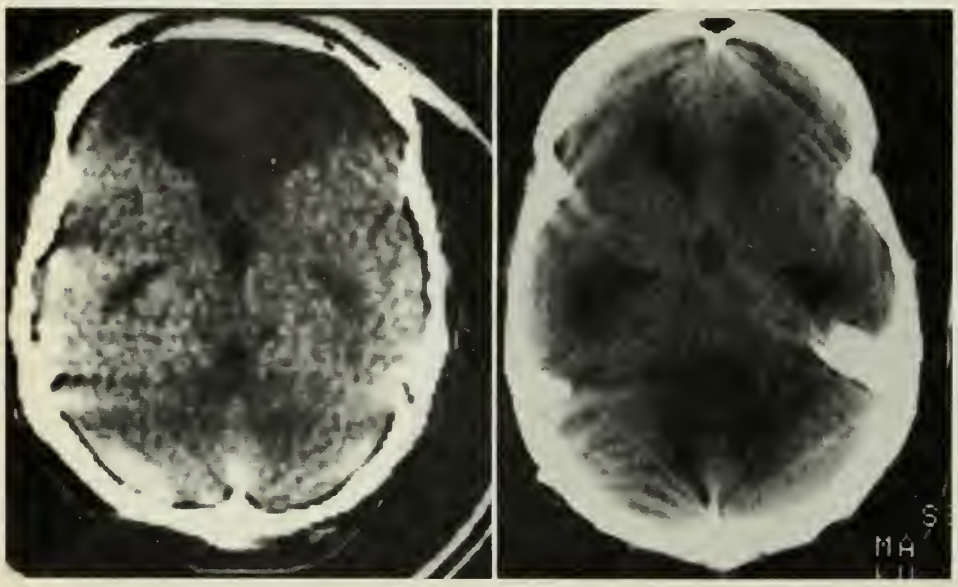

Figure 4.—**Left** and **Right,** Progressive dilatation of the fourth ventricle over a period of ten weeks. A ventriculoperitoneal shunt had been placed during the interim period.

Before the advent of chemotherapy with amphotericin B and ventricular shunting procedures, coccidioidal meningitis was usually fatal within one year of diagnosis.[6] Although these modalities have increased survival times and produced apparent cures in some patients, the disease continues to be associated with substantial mortality and morbidity.

In our study we sought to document the CT scan findings in 22 patients with coccidioidal meningitis and to determine whether this test could be used to predict prognosis. The characteristics of these patients with respect to age, sex, race, clinical presentation and evidence of the pathogen in cerebrospinal fluid were similar to those described in other reports on coccidioidal meningitis.

The most common findings were ventricular enlargement together with enhancement or obliteration of the basal cisterns, or both. Ventricular and cisternal abnormalities were usually seen in combination, though one patient had cisternal obliteration with normal-sized ventricles and another had generalized ventriculomegaly with no apparent cisternal changes.

These findings correlate well with known histopathologic changes in patients with coccidioidal meningitis. The fungal organism elicits a granulomatous meningitis with thickening and opacification of the basilar meninges. In later stages of the disease, the meninges around the brain stem may be completely replaced by a thick inflammatory exudate consisting of lymphocytes, plasma cells, multinucleated giant cells and coccidioidal spherules with endospores. Hydrocephalus develops when this inflammatory process produces obstruction in the subarachnoid space at the skull base or in the fourth ventricular outlet foramina.

Inflammation may also extend into the ventricular surface to produce a granular ependymitis. This accounts for the ependymal enhancement seen in one of our patients and probably explains the asymmetric ventricular enlargement seen in eight other patients. Ventriculitis beginning in the posterior fossa could produce complete or partial fourth ventricular obliteration (as it did in four patients) or focal dilatation of the fourth ventricle or temporal horn (seen in four patients), depending on the specific locus of ependymal proliferation. Acquired fourth ventricular enlargement after lateral ventricular shunting was noted in two patients. This has been described by others[7] and is presumably due to obstruction of the Sylvian aqueduct superimposed on a generalized hydrocephalus produced by the coccidioidal basilar exudate. Recognizing this phenomenon is important because a loculated fourth ventricle may act as a posterior fossa mass lesion and require surgical decompression.

Two of our patients had small hypodense areas in the subcortical white matter. Although cerebral angiograms were not obtained, vasculitis and cerebral infarction have been documented[8,9] in patients with coccidioidal meningitis caused by the intense inflammatory response around the vessels at the circle of Willis.

The only previous report describing CT scan findings in a large number of patients with coccidioidal meningitis is that of Dublin and Phillips.[10] Their observations in 15 patients are in agreement with our experience regarding the high incidence of ventriculomegaly and cisternal abnormalities. Only one of their patients had a normal scan and they found white matter lesions in six patients. This contrasts with our series in which six of the patients had a normal scan and two had scans showing hypodense areas in the white matter. These differences may be explained by the timing of CT scanning: in our study a CT scan was done when an initial diagnosis was made rather than later in the course of the disease. Their series also differed from ours in failing to note instances of asymmetric ventricular enlargement, a frequent occurrence in our group of patients.

Tuberculous meningitis,[11,12] meningeal carcinomatosis,[13–15] intracranial cysticercosis,[16] other types of fungal meningitis[17,18] and *Hemophilus influenzae* meningitis[19] have all produced CT scan abnormalities similar or identical to those in cases of coccidioidal meningitis. Although the incidence of hydrocephalus may be slightly greater with coccidioidal meningitis, there are no clear-cut radiographic features that allow this disease to be differentiated from other forms of basilar meningitis on the basis of CT scan findings alone. Such a distinction relies on additional information, including the findings in cerebrospinal fluid specimens, and a history of travel or residence in endemic areas.

A correlation was found between initial CT scan findings in patients with coccidioidal meningitis and their subsequent course. Those with normal scans were likely to have signs and symptoms confined to meningeal irritation, while those with abnormal scans were more apt to have evidence of increased intracranial pressure or impaired mentation. Of greater importance was the fact that patients whose CT scans were normal at the time a diagnosis was established seemed to have a better long-term prognosis than persons with abnormal scans. Only one of six patients (17%) with a normal scan has died and the other five (83%) are living independent lives. In the group with abnormal scans, five died (a 31% mortality rate) and seven (44%) are living independent lives. Currently, cure rates in the two groups cannot be assessed as most patients are still undergoing active treatment and their eventual outcome is unknown. Although follow-up intervals differed and treatment protocols were not standardized, the aforementioned observations indicate that initial CT scan findings in patients with coccidioidal meningitis may provide some insight into their subsequent clinical course.

In conclusion, we believe the CT scan is a useful modality in the diagnosis and follow-up of patients with coccidioidal meningitis. Initial CT scans should be done both with and without contrast enhancement, as this may disclose subtle cisternal or ependymal abnormalities not apparent on unenhanced scans alone. Contrast enhancement can usually be avoided in subsequent studies to assess ventricular size when a diagnosis of coccidioidal meningitis has already been established. Although a normal CT scan does not exclude the presence of coccidioidal meningitis, it does indicate a more favorable prognosis for those who have the disease. Serial CT scans help to select patients who will require ventricular drainage and are essential to identify patients in whom fourth ventricular loculation develops after lateral ventricular shunting.

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Medical Practice Question

EDITOR'S NOTE: *From time to time medical practice questions from organizations with a legitimate interest in the information are referred to the Scientific Board by the Quality Care Review Commission of the California Medical Association. The opinions offered are based on training, experience and literature reviewed by specialists. These opinions are, however, informational only and should not be interpreted as directives, instructions or policy statements.*

Computed Tomography/Multiplanar Reformation

QUESTION:

Is computed tomography/multiplanar reformation an accepted medical practice for the diagnosis of spinal disorders or is it considered investigational?

OPINION:

In the opinion of the Scientific Advisory Panel on Radiology, computed tomography/multiplanar reformation is considered an accepted, but not routine, medical practice for the diagnostic evaluation of lumbar spine disorders. This technique adds valuable information in certain cases of trauma to the spine and in selected other diagnostic situations where transaxial scans are judged inadequate, but it should be used on an individual case basis. It is not suggested as a general approach to a limited disc/radicular pain syndrome that is limited to one level.

In the vast majority of patients, a satisfactory diagnosis of pathologic conditions can be obtained using the usual primary axial images obtained by computed tomography. Finally, it was observed that most modern third and fourth generation computed tomography scanners can provide images comparable to multiplanar reformation images, with some minor exceptions, such as the "curved coronal images."

Medical Progress

Paraneoplastic Syndromes of the Nervous System

GEORGE PALMA, MD, *Sacramento, California*

The paraneoplastic disorders of the nervous system are clinicopathologic syndromes that occur in association with systemic cancer. Dysfunction of any part of the nervous system or its effector organs may be produced by a paraneoplastic process. The temporal relationship between the onset of a paraneoplastic syndrome and the diagnosis of the associated cancer varies. Most of the paraneoplastic syndromes of the nervous system may appear months to years before the cancer is discovered. The pathogenesis of most of the paraneoplastic syndromes of the nervous system is unknown and specific, effective therapy is lacking. With rare exceptions, treatment of the associated cancer seldom alters the course of patients with these syndromes. However, in other paraneoplastic syndromes such as myasthenia gravis, myasthenic syndrome of Eaton-Lambert and polymyositis-dermatomyositis an autoimmune pathogenesis is established or strongly suspected.

(Palma G: Paraneoplastic syndromes of the nervous system [Medical Progress]. West J Med 1985 Jun; 142:787-796)

Paraneoplastic syndromes of the nervous system are clinicopathologic syndromes that occur more frequently in association with systemic cancer than can be accounted for by chance and which are not caused by neoplastic invasion of the nervous system or by antineoplastic therapy. Each of the paraneoplastic syndromes may occur in patients who never have cancer, and many of them are found more often in patients without neoplasia.

In about 15% to 20% of patients who have cancer, a symptomatic nervous system disorder develops during the course of their illness.[1,2] Most often the neurologic symptoms are the result of direct invasion of the nervous system by primary or metastatic tumor,[2] but a variety of other disease mechanisms may be the cause of neurologic disability (Table 1). The paraneoplastic syndromes collectively account for about 10% of the neurologic morbidity in patients with cancer.[2] The recognition of these syndromes and inquiry into their pathogenesis and treatment are important for several reasons.

Because the signs and symptoms of paraneoplastic syndromes commonly precede those of an associated neoplasm, they may be considered clinical markers of a heightened vulnerability for the development of cancer. The appearance of a paraneoplastic syndrome in a patient alerts the physician to the possibility of an undiscovered malignant lesion and enables the physician to institute appropriate evaluation and surveillance of an affected patient so that an occult neoplasm may be diagnosed as early as possible.

Many of the syndromes to be described below produce severe disability in patients who would otherwise lead reasonably normal lives. Successful treatment of paraneoplastic syndromes would certainly improve the quality of life for these patients and conceivably enhance survival as well. Finally, the study of paraneoplastic processes provides us with an opportunity to view the relationship between a malignant neoplasm and its "host" patient. From this perspective, concepts of cancer vulnerability and mechanisms of disease are likely to expand when more is learned about the pathogenesis of paraneoplastic syndromes.

The classification of paraneoplastic syndromes of the nervous system used in this review (Table 2) has been modified from that presented in the monograph by Henson and Urich.[3] For the most part the classification is based on the topography of the pathologic abnormalities of each syndrome, beginning with the central nervous system and moving peripherally. For each syndrome the epidemiology, clinical features, results of selected laboratory tests, neuropathology, treatment and pathogenesis are described.

Cerebellar Disorders

There are two cerebellar syndromes that occur in patients with malignant disease (see Table 2). They are both rare and among the least common paraneoplastic syndromes of the nervous system.[3]

A cerebellar cortical degeneration occurs in adult patients with cancer of many types. Most reported cases have been in

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ABBREVIATIONS USED IN TEXT

CSF = cerebrospinal fluid
CT = computed tomography
EEG = electroencephalogram
EMG = electromyography

association with cancer of the lung and ovary, but the syndrome has also been described with Hodgkin's and non-Hodgkin's lymphoma and cancer of the breast, uterus, stomach, colon and larynx.[3-7] The precise incidence of paraneoplastic cerebellar degeneration is unknown.

In most patients the cerebellar disorder makes its appearance before the associated cancer is diagnosed. The interval between the onset of neurologic symptoms and the diagnosis of cancer ranges from 1 month to 8 years, with a mean interval of 20 months.[5] The signs and symptoms of this syndrome may appear abruptly but usually evolve over several weeks and occasionally months. The initial manifestations consist of ataxia of limbs, gait ataxia, dysarthria and nystagmus.[3,5] Opsoclonus, which is an abnormal movement of the eyes characterized by rapid and chaotic conjugate eye movements, has also been described.[7-9] Often the symptoms and signs attributable to cerebellar degeneration are found in combination with those of other neurologic paraneoplastic syndromes.[5,8,10]

The diagnosis of this disorder relies on the discovery of the associated cancer in the face of the typical clinical features of cerebellar degeneration. Cerebrospinal fluid (CSF) is abnormal in more than half of the cases, with the most common abnormalities being lymphocytic pleocytosis and an elevated protein level.[5,7,8,10,11] In addition, elevated levels of CSF immunoglobulin and abnormal colloidal-gold curves have been described.[5,8,10] Cerebellar atrophy has been shown by computed tomography in only one patient with cerebellar degeneration associated with Hodgkin's disease.[6] Unfortunately, in some cases the associated cancer remained undiagnosed until autopsy.[5,8]

The main pathologic finding in paraneoplastic cerebellar degeneration is the loss of Purkinje cells from the cerebellar cortex.[3,5,7,8,10] Rarely is there gross cerebellar atrophy.[3] In some cases of this disorder the pathologic changes of encephalomyelitis are seen as well (see below).[3,5,8] Paraneoplastic cerebellar degeneration occurs more frequently than the analysis of patients with clinical signs would suggest. In a morphometric study of the cerebellar cortices obtained postmortem from patients who had died of cancer but who had had no evidence of cerebellar disease in life, there was a significant loss of Purkinje cells.[12] This was particularly striking in women with ovarian cancer. The cellular loss was less pronounced than that found in patients with the clinical syndrome, suggesting that an asymptomatic cerebellar degeneration does occur.

With rare exceptions[11] the clinical manifestations of paraneoplastic cerebellar degeneration are not altered by successful treatment of the associated neoplasm.[3-5] Although empirical treatment with the use of vitamins and immunosuppressive drugs is not generally helpful, in one instance neurologic improvement occurred when the patient was given thiamine.[9]

Several observations suggest that paraneoplastic cerebellar degeneration is an immune-mediated disorder. In many cases of the syndrome there are elevated levels of CSF γ-globulin or immunoglobulin.[4,5,10] In a patient with ovarian carcinoma and autopsy-proved cerebellar cortical degeneration, the CSF contained antibodies that bound to neonatal mouse cerebellar cells.[10] A patient with Hodgkin's disease and a clinical cerebellar syndrome had serum antibodies that stained human cerebellar Purkinje cells.[4] Two women with ovarian cancer and autopsy-confirmed cerebellar degeneration had high titers of serum immunoglobulin G (IgG) that reacted with human Purkinje cells and cells of the deep cerebellar nuclei, but no other antigens derived from neural or nonneural tissues.[13] High titers of serum antibody with the same specificity were also found in 2 of 14 women who had ovarian cancer but no neurologic symptoms. However, it cannot be proved that the antibodies found in these cases were the cause of the neurologic syndrome. Rather, they may be the result of Purkinje cell injury produced by some other mechanism.

The second paraneoplastic cerebellar syndrome—myoclonic encephalopathy—is found in 2% to 7% of children with neuroblastoma.[14,15]

Usually the onset of myoclonic encephalopathy occurs

TABLE 1.—*Causes of Neurologic Disorders in Patients With Cancer*

Involvement of the nervous system by tumor
Primary
Metastatic
Adverse effects of drug and radiation therapy
Opportunistic infections
Metabolic and endocrinologic disorders
Cachexia and nutritional deficiencies
Paraneoplastic syndromes
Diseases unrelated to cancer

TABLE 2.—*Paraneoplastic Syndromes of the Nervous System*

Cerebellar syndromes
Cortical cerebellar degeneration
Myoclonic encephalopathy
Encephalomyelitis
Limbic encephalitis
Brain-stem encephalitis
Poliomyelitis
Dorsal root ganglionitis
Cerebrovascular diseases
Disseminated intravascular coagulation
Cerebral venous thrombosis
Nonbacterial thrombotic endocarditis
Subacute necrotizing myelopathy
Peripheral polyneuropathy
Sensory
Sensorimotor
Neuromuscular junction
Myasthenia gravis
Myasthenic syndrome of Eaton-Lambert
Skeletal muscle
Polymyositis-dermatomyositis
Carcinomatous "neuromyopathy"
Cachexia

before a neuroblastoma is diagnosed. The interval between the onset of the neurologic disorder and the discovery of a neuroblastoma may range from weeks to years with an average of about two months.[14,16,17] The clinical manifestations are dramatic and fairly constant from case to case. There is an acute or subacute onset of irritability, ataxia of gait and limbs, polymyoclonus and opsoclonus in a child who was previously well.[14-19] Most of the children are younger than 2 years at the time of onset.[14]

Diagnosis must be made on clinical grounds. Results of CSF examination and the electroencephalogram (EEG) are almost always normal.[15,17,19] In a few cases pneumoencephalography has shown signs of cerebellar atrophy.[18,19] In about half of the patients there is an elevation of urinary catecholamines or their metabolites at the time of onset.[18] This finding reflects the secretory activity of the associated neuroblastoma.

The pathologic features of myoclonic encephalopathy have not been systematically studied. There is a report of demyelination around the dentate nuclei of the cerebellum in one case.[18] Other cases that have come to autopsy have had no neuropathologic abnormality.[3]

The management of patients with myoclonic encephalopathy is directed towards finding the associated neuroblastoma and instituting appropriate antineoplastic therapy. There may be spontaneous remissions and relapses of the neurologic symptoms and remission following successful therapy for the associated neuroblastoma.[15,17,19] Treatment with adrenocorticotropic hormone and adrenal corticosteroids is usually effective in ameliorating neurologic abnormalities, but the patients' clinical response may be incomplete,[15,16,19] and the symptoms may return on withdrawal of the drug regimen.[19] Despite treatment, most patients will have long-term neurologic sequelae that include ataxia and mental retardation.[15,17,18] Children with both neuroblastoma and myoclonic encephalopathy have a longer survival rate than do children with only neuroblastoma.[14] The pathogenesis of myoclonic encephalopathy is not known.

Encephalomyelitis

Paraneoplastic encephalomyelitis is an inflammatory disorder of brain and spinal cord that predominantly affects gray matter structures. It most often occurs in patients with oat cell carcinoma of the lung but has also been described in patients with other types of lung cancer and carcinoma of the breast, ovary, stomach and uterus and Hodgkin's disease.[20-28] In a large series of patients with lung cancer this disorder was found in 0.36%.[3] The symptoms of encephalomyelitis usually appear before the associated cancer is diagnosed, and in some patients with oat cell carcinoma of the lung, the cancer is found only at autopsy.[3,21,23]

Although Table 2 lists four types of encephalomyelitis, this classification is based on the topography of the neuropathologic findings. In fact, a review of the clinical and pathologic findings of reported cases makes it quite clear that rarely do any of these four types appear in isolation. In most patients there is clinical and pathologic involvement of two or more regions of brain or spinal cord.[3,22]

In each type of paraneoplastic encephalomyelitis, the onset of symptoms is acute or subacute and patients tend to worsen over weeks or months.[21-23,26,29] Once the encephalomyelitis is fully developed there is generally no resolution of the condition. While patients may survive for as long as two years with encephalomyelitis, the mean duration of illness is less than a year.[22]

In patients with limbic encephalitis the appearance of mental changes or seizures is usually the first manifestation of the disease.[23,24,27,29] Restlessness, anxiety, depression, hallucinations and a striking impairment of memory are common.[23,27,29] The seizures are most often generalized convulsive (grand mal) or partial complex (psychomotor) in type. As the disease progresses the patient may be left demented and totally disabled, although there are patients who experience an arrest of the disease at some point short of total disability.[23,24,29]

The symptoms of patients with brain-stem encephalitis vary with the region of the brain stem that is most severely involved. Patients in whom the pons and medulla are the sites of major involvement will have vertigo, loss of hearing, facial numbness and difficulty with swallowing and speech articulation. Relevant signs in these patients include nystagmus, impaired facial sensation, sensorineural hearing loss, dysarthria and weakness and atrophy of tongue and palatal muscles.[3,22,24] Ptosis, ophthalmoplegia, conjugate gaze palsies and abnormal involuntary movements are found in patients with encephalitis of the diencephalon or midbrain.[22,24,26]

When the spinal cord is the site of disease a form of poliomyelitis results. In this syndrome there is progressive weakness and atrophy of skeletal muscles, associated with muscle fasciculations and diminished or absent muscle stretch reflexes.[20-22,24] Weakness may be widespread and bilateral or it may be asymmetric. The signs and symptoms of paraneoplastic poliomyelitis may resemble those of the more common types of degenerative diseases of motor neurons such as amyotrophic lateral sclerosis and progressive spinal muscular atrophy. However, there is no convincing evidence that these latter diseases occur at a higher than expected frequency in patients with cancer.[30] Usually paraneoplastic poliomyelitis can be distinguished from the degenerative motor neuron diseases on clinical grounds.

A form of motor neuron disease that differs from the usual paraneoplastic poliomyelitis has been described in patients with lymphoma, most of whom had undergone spinal cord irradiation before the onset of weakness.[31,32] Although the symptoms and signs of this syndrome are the same as those of paraneoplastic poliomyelitis, the clinical course is milder and full neurologic recovery may occur. Whether this so-called subacute motor neuronopathy is a distinct disease entity or a variation of paraneoplastic poliomyelitis is not clear at this time.

Dorsal root ganglionitis, the fourth type of paraneoplastic encephalomyelitis, is in fact a disease of the peripheral nervous system. It is described in this section because it occurs in patients with the other types of encephalomyelitis and the pathologic abnormalities found in ganglionitis are identical to those of encephalomyelitis. The earliest symptoms are unsteadiness of gait and paresthesias, numbness and pain in the distal limbs.[28,33] All patients show sensory loss and diminished or absent muscle stretch reflexes on examination.[28,33] Loss of sensation virtually always includes impairment of all primary sensory modalities.[28] About half of the patients with ganglionitis also have mental changes, cranial nerve dysfunc-

tion or weakness—signs that indicate that the disease process affects more than the sensory ganglia.[28]

There is no laboratory abnormality specific for any type of encephalomyelitis. Nevertheless, certain studies are useful as aids in the diagnosis of the different types of this disease. In most patients with any type of encephalomyelitis the CSF is abnormal.[3,22,23,25,27-29] A lymphocytic CSF pleocytosis or an elevation of the protein content is frequently found, and both may occur together.[3,22] In patients with limbic encephalitis the EEG is usually abnormal. Most often slow waves and epileptiform activity are recorded over one or both temporal lobes. A generalized slowing and disorganization of background rhythms may also be seen.[3,21,23,27,29] In the poliomyelitic form, electromyography (EMG) and a muscle biopsy specimen will show the electrophysiologic and histologic abnormalities of muscle denervation, respectively.[20,21,32] Finally, sensory nerve conduction velocities were unobtainable in the few cases of ganglionitis studied.[28]

Regardless of the type of encephalomyelitis, the neuropathologic findings are the same; only the site of maximal involvement differs among the four types.[3,20-24,26,28,29,33] The major abnormality found is inflammation, which consists mainly of infiltration of lymphocytes and occasionally plasma cells around blood vessels. Loss of neurons and proliferation of reactive astrocytes are also prominent pathologic features. Because of neuronal loss there may also be secondary degeneration of fiber tracts. In limbic encephalitis the histologic abnormalities are located in mesial temporal lobe structures such as the amygdala, hippocampus and uncus and in the insula and cingulate gyrus.[23,24,29] In brain-stem encephalitis the cranial nerve nuclei, inferior olivary nuclei, substantia nigra and other brain-stem nuclei are the site of the inflammation.[21,22,24,26] In poliomyelitis and ganglionitis the anterior gray horns of the spinal cord and the dorsal root ganglia, respectively, are affected by the inflammatory process.[20-22,24,28,33] In the latter type there is also a prominent degeneration of the dorsal white columns of the spinal cord.

There is no effective therapy for patients with any type of paraneoplastic encephalomyelitis. Even successful treatment of the associated neoplasm usually does not alter the course of the neurologic disease, though exceptions have been reported.[27]

The pathogenesis of paraneoplastic encephalomyelitis is not known. The neuropathologic features of this disorder resemble those of viral encephalomyelitis. However, viral inclusions have not been seen by light microscopy.[23,24] In a patient with Hodgkin's disease and paraneoplastic poliomyelitis, postmortem examination of the spinal cord by electron microscopy showed particles that morphologically resembled virions within motor neurons.[20] Attempts to culture virus from dorsal root ganglia obtained after death from four patients with ganglionitis were unsuccessful, and no viral particles could be found by electron microscopy.[28] An immune-mediated injury of the nervous system is suggested by the finding of antibodies to central nervous system tissues in the serum of four patients with oat cell carcinoma of the lung and dorsal root ganglionitis.[33] This could not be duplicated in other patients with the same disorder, however.[28] The frequent occurrence of an abnormal colloidal-gold reaction in CSF and elevation of CSF γ-globulin levels in patients with paraneoplastic encephalomyelitis is consistent with either a viral or an immune-mediated cause.[22,25,29]

Vascular Syndromes

Three vascular paraneoplastic syndromes occur in patients with cancer (see Table 2). In each syndrome the neurologic symptoms are the result of brain ischemia and infarction caused by focal or multifocal vascular occlusions.

Disseminated intravascular coagulation is found at autopsy in 0.8% of patients with cancer.[34] It is most frequently found in patients with lymphoma and leukemia. In a study of autopsy cases selected because of the presence of disseminated intravascular coagulation, about 40% of the patients had cancer.[35]

The neurologic manifestations of this coagulation disorder consist of signs of both focal and generalized brain dysfunction.[34,35] Signs of generalized brain ischemia, which are present in virtually all patients with disseminated intravascular coagulation, include confusion or delirium, depressed levels of consciousness, generalized convulsive seizures and asterixis. In addition, more than half of the patients have signs of focal cerebral ischemia such as hemiparesis, aphasia, ataxia, cranial neuropathies, cortical blindness and focal motor seizures.[34,35]

Laboratory tests of hemostatic function are the most helpful studies in establishing the diagnosis of disseminated intravascular coagulation. There are demonstrable abnormalities of clotting function present at some point in the course of virtually every patient. The abnormalities, which occur alone or in various combinations, include prolonged prothrombin times, low levels of plasma fibrinogen, thrombocytopenia and the presence of fibrin-degradation products.[34-36]

The neuropathologic basis for the clinical findings in disseminated intravascular coagulation is multiple hemorrhagic and bland infarctions of the brain produced by widespread occlusion of arterioles, capillaries and veins by fibrin thromboses.[34,35] The infarcts vary considerably in size and occur in cerebral cortex more frequently than in white matter. Subarachnoid bleeding may also be found.[35]

The second vascular syndrome is thrombosis of cerebral veins and dural venous sinuses. In an autopsy study, two thirds of sinovenous thromboses that occur in this population of patients are caused by metastasis to dural venous sinuses or adjacent structures. The remaining third have no demonstrable metastatic disease to account for the thromboses.[37] Like disseminated intravascular coagulation, nonmetastatic venous thromboses appear to occur most frequently in patients with leukemia and lymphoma, though patients with breast and lung cancer make up about a third of the cases.[37,38]

The symptoms and signs of sinovenous thromboses are produced by two different mechanisms: cerebral ischemia and infarction, and raised intracranial pressure due to impaired bulk resorption of cerebrospinal fluid.[37,38] The onset of symptoms is usually abrupt. There is headache in most patients, and hemiparesis, sensory loss, aphasia, visual field defects, altered mental function and focal and generalized seizures are common.[38]

Although the diagnosis of cerebral venous thrombosis may be suspected in patients with cancer in whom the typical symptoms and signs develop, confirmation requires laboratory tests. Many patients have abnormal clotting values sim-

ilar to those described above for disseminated intravascular coagulation.[37,38] Results of a CSF examination are usually abnormal. Most often there is an elevated opening pressure and the CSF shows an excess number of erythrocytes.[38] Grossly bloody CSF may occur, as may elevation of the protein level and a modest pleocytosis. Because the EEG is usually abnormal, it has been suggested as a screening test for sinovenous thrombosis.[38] Focal and generalized slow-wave abnormalities are the most common EEG findings. Computed tomography (CT) of the head is most useful in excluding metastatic disease as a cause of a patient's clinical syndrome, but in about 25% of patients it will show abnormalities that are specific for sinovenous thrombosis.[39] Generally, however, cerebral arteriography is required to confirm the diagnosis of this disorder. Intravenous arteriography using the digital subtraction technique is capable of showing the occluded cerebral sinuses and veins.[40]

The pathologic findings in this disorder include thrombosis of the superior sagittal sinus, the vein of Galen and cortical veins and brain edema and hemorrhagic brain infarction.[38] Usually there are several areas of hemorrhage, which can result in cerebral herniation through the tentorium cerebelli or the foramen magnum.[38]

There is no therapy that is known to be effective in treating of cerebral venous thrombosis. Anticoagulation with heparin is of unproved efficacy and it has the potential of increasing the risk of brain hemorrhage. Its use should be considered only in those patients who have confirmed sinovenous thrombosis and in whom there is no evidence of intracranial bleeding on CT and CSF examination. Symptomatic treatment of seizures and intracranial hypertension may be helpful but does not alter the underlying pathologic process.

The true mortality rate of paraneoplastic sinovenous thrombosis is not known but the available data indicate that about 50% of patients will recover at least transiently.[37,38] In one series no patient who went into coma survived.[38]

The third vascular syndrome that is found in patients who have cancer is nonbacterial thrombotic endocarditis, which is also known as marantic endocarditis. In a large general autopsy series, nonbacterial thrombotic endocarditis was present in 0.7% of the cases.[41] Of the patients who had nonbacterial thrombotic endocarditis, 42% also had cancer. Other studies have found a coincidence of cancer in 36% to 75% of patients with this condition.[42,43] Adenocarcinoma was present in 60% of the patients with both nonbacterial thrombotic endocarditis and cancer, and hematologic or lymphoproliferative malignant lesions were found in 21%.[41]

The clinical hallmark of this form of endocarditis is the occurrence of embolic infarction of brain and other organs. Stroke occurs in 33% to 50% of patients with this disorder, and in most of these patients there are multiple cerebral infarctions.[41,42] Infarctions also frequently occur in kidney and spleen and less commonly in gut, liver, heart and limbs.[41,43] About 22% of patients also have thrombophlebitis.[42]

The diagnosis of nonbacterial thrombotic endocarditis may be very difficult to confirm. Signs of cardiac disease may be minimal, and, in fact, a heart murmur is present in less than a third of the patients who have this type of endocarditis.[41,42] Although echocardiography may show the thrombi of nonbacterial thrombotic endocarditis,[44,45] generally it has not been helpful.[41] Thrombocytopenia, hypofibrinogenemia and abnormal prothrombin times may be found.[42] Blood cultures are sterile. In the absence of a specific confirmatory test, the diagnosis must be made on clinical grounds after other causes of multiple emboli, such as infectious endocarditis and rheumatic heart disease, have been excluded.

Pathologic examination in cases of nonbacterial thrombotic endocarditis shows multiple small, sterile thrombi on the cardiac valves.[41-43] The thrombi, which are composed of fibrin and platelets, may form on any valve but are most frequently found on the aortic and mitral valves.[42] In the brain there are multiple infarcts, which may be hemorrhagic or bland in appearance and which may vary considerably in size.[41,42]

There is no uniformly effective medical therapy for nonbacterial thrombotic endocarditis, although anticoagulation with heparin may help prevent recurrence of emboli. Heparin, of course, is contraindicated in patients with hemorrhagic stroke. Operative replacement of an involved heart valve was effective in preventing recurring emboli in one patient.[44]

Each of the three paraneoplastic vascular syndromes seems to have in common a disturbance of hemostasis that has been characterized as a hypercoagulable state.[36] The pathogenesis of this hypercoagulability and the reason for the occurrence of three distinct clinical syndromes in association with it are not well understood.[36,38]

Subacute Necrotizing Myelopathy

Necrotizing myelopathy is a very rare paraneoplastic disorder. The exact incidence is not known. It has been reported to occur in patients with lung cancer, lymphoma and carcinoma of the breast, kidney, thyroid, ovary, stomach and prostate.[46-49] This syndrome has also been observed in a patient with lung cancer who also had paraneoplastic cerebellar degeneration.[49]

In about half of the cases of subacute necrotizing myelopathy, the neurologic syndrome develops before the associated cancer is diagnosed.[48] As the name implies, the clinical symptoms and signs evolve over days to weeks.[46,48] The myelopathy begins with pain and paresthesias in the lower limbs and progresses over days to produce paraparesis and paralysis of urinary sphincter function. Loss of all modalities of sensation below the midthoracic region generally follows closely on the development of weakness. The disorder progresses over a week or two as the segmental level of lost motor and sensory function ascends to the cervical region. Dysautonomia may also be a prominent feature in the latter stages of this disorder.[48]

Contrast myelography may show fusiform enlargement of the spinal cord but may also be normal.[46] The myelogram is most useful in excluding the presence of the more common syndrome of spinal cord compression by extradural metastases. CSF abnormalities, which are not specific to necrotizing myelopathy, include an excess of erythrocytes and leukocytes and elevation of the protein level.[46,48,49]

The principal neuropathologic finding of necrotizing myelopathy is necrosis of all histologic elements of the spinal cord. Necrosis extends over many cord segments and it tends to be most severe in the midthoracic segments.[48] No evidence of vascular occlusion or inflammation has been described and the pathogenesis of this syndrome remains unknown.[2]

There is no effective treatment for patients with paraneoplastic necrotizing myelopathy. With only rare exceptions virtually all patients with this syndrome die.[47,48] A median survival of five weeks has been reported.[47]

Peripheral Neuropathy

Peripheral polyneuropathy is the most common paraneoplastic syndrome. It occurs in about 5% of patients with lung cancer and in 1% to 3% of patients with carcinoma of the stomach, breast and colon.[3] Symptomatic peripheral neuropathy is common in patients with malignant plasma cell dyscrasias (3.6%) and lymphoma (8%).[50,51] Neuropathy has also been reported in patients with Hodgkin's disease, carcinoid tumor and carcinomas arising from a variety of sites including pancreas, uterus, mouth, kidney and bladder.[51-55] A particularly striking association has been described between solitary plasmacytoma and peripheral neuropathy.[56-58] Nerve conduction studies carried out on patients with different types of cancer have shown prevalences of 35% to 50% of asymptomatic neuropathy.[3,51] About half the time the neuropathy appears before the associated cancer is diagnosed,[55] although in one series of patients with plasmacytoma the peripheral neuropathy appeared first in 95% of the patients.[58]

Paraneoplastic peripheral neuropathy may be sensory or mixed sensory and motor in type. The less common sensory neuropathy is in fact dorsal root ganglionitis (see above) and will not be further discussed here. The onset of symptoms of the sensorimotor neuropathy may be acute (and indistinguishable from the Guillain-Barré syndrome), subacute or chronic, and the course may be one of progressive clinical deterioration or may be punctuated by remissions and relapses.[52,55] Most often the clinical manifestations of paraneoplastic neuropathy do not differ from sensorimotor neuropathy associated with other systemic diseases. The most common symptoms and signs are weakness and sensory symptoms such as paresthesias, numbness and pain that begin in the distal parts of the limbs. Muscle stretch reflexes are absent or decreased and atrophy is seen especially in distal muscles.

On occasion patients with paraneoplastic neuropathy present in an unusual manner. Neuromyotonia, a clinical syndrome characterized by muscle stiffness, widespread fasciculations and high frequency discharges on EMG, has been the initial manifestation of neuropathy in patients with lung cancer.[59,60] Similarly, dysautonomia may be the major manifestation of paraneoplastic neuropathy associated with oat cell carcinoma of the lung.[61,62]

Several laboratory tests are helpful in confirming the diagnosis of peripheral neuropathy, but none are specific for the paraneoplastic variety. Results of nerve conduction studies are generally abnormal. The abnormalities include prolongation of distal sensory and motor latencies, slowing of conduction velocities and decreased amplitude of evoked compound muscle action potentials in various combinations.[51,54,56,58,63,64] Most patients with paraneoplastic neuropathy have an elevation of the CSF protein level but no excess of cells.[55,56,58,63,64]

Sural nerve biopsy specimens and postmortem examination of peripheral nerves from patients with paraneoplastic neuropathy usually show segmental demyelination, particularly in the acute and relapsing forms.[3,51,55,58] In cases of long-standing neuropathy and in the chronic form of paraneoplastic neuropathy, there is axonal degeneration in addition to demyelination.[3,55] Occasionally a lymphocytic inflammatory infiltrate is also noted in nerve.[55]

There is no uniformly effective therapy for paraneoplastic peripheral neuropathy. In some patients with visceral cancers, treatment of the neoplasm may result in abatement of the neuropathic symptoms,[53,54] but this is not usually the case. In patients with a relapsing and remitting form of sensorimotor neuropathy, remission has occurred during treatment with adrenocorticosteroid drugs.[55] Finally, in patients with plasmacytomas, treatment with tumoricidal irradiation or with prednisone has resulted in improvement in patients' neuropathic condition.[56,58]

The cause of paraneoplastic neuropathy is not known and may, in fact, vary according to the type of neuropathy and the type of associated neoplasm. The similarity between the sensorimotor neuropathy and idiopathic inflammatory polyneuropathy suggests that nerve injury is produced by immune mechanisms.[52,65] Deposition of immunoglobulin (IgM) and complement has been described in the sural nerves of patients with cancer and sensorimotor neuropathy.[63] Deposition of IgM on myelin sheaths has also been seen in the sural nerve of a patient with a demyelinating peripheral neuropathy associated with Waldenström's macroglobulinemia.[64] It is not clear at this time, however, if the evidence cited is the cause of the neuropathy or a reaction to nerve injury produced by some other mechanism.

Disorders of the Neuromuscular Junction

There are two disorders of neuromuscular transmission that occur in patients with malignant neoplasia. The first, myasthenia gravis, occurs in association only with thymoma.[3,66] The second is the myasthenic syndrome of Eaton-Lambert, which occurs in patients with a variety of cancers.[3]

Between 10% and 20% of patients with myasthenia gravis have thymoma, and about 30% of patients with thymoma have myasthenia gravis.[67-70] In most patients who have both diseases, myasthenia gravis develops first, but it occurs in about 12% of patients after thymectomy for thymoma.[69] About 75% of the thymomas found in association with myasthenia gravis occur in patients older than 40 years.[68] About half of the thymomas that occur in association with myasthenia gravis are found to be invasive at the time of thymectomy.[68] Although myasthenia gravis has been described in patients with neoplasms other than thymoma, the association appears to be accidental.[3]

Pathologic fatigability of muscle is the hallmark of myasthenia gravis.[66,71] Weakness that develops after sustained muscular activity or repetitive muscle contraction is the clinical expression of the fatigability. Strength is restored, at least partially, by rest and by the injection of an acetylcholinesterase inhibitor.[66,71] The most frequently affected muscles are the muscles of ocular movement,[66] but any skeletal muscle may be involved. Muscle stretch reflexes are generally normal and sensory symptoms virtually never occur in patients with myasthenia gravis.[66]

The diagnosis may be confirmed in several ways. First, the finding that muscle weakness can be produced easily by sustained or repetitive contraction and that weakness can be rapidly reversed by the intravenous administration of edrophonium chloride or neostigmine methylsulfate confirms the

diagnosis.[66,71] Confirmation can also be made by repetitive nerve stimulation studies which, in a case of myasthenia gravis, show a decrement in the amplitude of the compound muscle action potential during low frequency stimulation.[66,71] The temporary repair of this electrophysiologic abnormality can be produced by administering edrophonium or neostigmine.[66,71] Finally, about 85% to 90% of patients with myasthenia gravis have serum antibodies to muscle acetylcholine receptor.[66,71-73]

Detection of thymoma has been improved by computed tomography of the thorax. This technique is more sensitive than plain chest radiography but is also less specific and will detect hyperplastic and normal thymuses as well as thymomas.[74] The two techniques should be considered complementary.

While a detailed discussion of the therapy for myasthenia gravis is beyond the scope of this review, a few remarks are in order.* Treatment with acetylcholinesterase inhibitors continues to be the standard.[66,71] However, this form of treatment does not correct the underlying dysimmune state (see below). Thymectomy, on the other hand, leads to complete remission of the disease in 50% to 60% of the patients and is associated with a lower mortality than is therapy with esterase inhibitors.[69,75] Patients who fail to achieve a full remission after thymectomy or who are not candidates for thymectomy may achieve remission with immunosuppressive therapy with prednisone or azathioprine.[66,71] Finally, plasmapheresis may improve the condition of patients with myasthenia gravis but its effects may be transient.[76-78] Plasmapheresis is probably most useful in treating patients in myasthenic crisis who are unresponsive to other forms of therapy. Patients who have thymoma have a much lower rate of remission of myasthenic symptoms and a lower five-year survival rate following thymectomy than do patients with normal or hyperplastic thymus glands.[68,70]

Failure of neuromuscular transmission occurs in cases of myasthenia gravis because of autoimmune injury to muscle acetylcholine receptors by antibody and, probably, cell-mediated immune mechanisms as well.[66,71,72,79,80] The thymus appears to play an important role in the development of myasthenia gravis.[73]

Although the myasthenic syndrome of Eaton-Lambert was initially described in patients with bronchogenic carcinoma,[81,82] it is now clear that in many patients with this syndrome, cancer never develops.[3,82,83] In addition to lung cancer, the myasthenic syndrome of Eaton-Lambert has been described in patients with lymphoma and with carcinoma of the breast, prostate, stomach and rectum.[3] Symptoms of the syndrome usually precede those of an associated cancer.[3]

Although the pathophysiology of the myasthenic syndrome of Eaton-Lambert resembles that of myasthenia gravis, the disorders differ clinically. Whereas pathologic fatigability of muscle occurs in patients with myasthenic syndrome, this symptom is not as prominent as in those with myasthenia gravis. Usually, the presenting symptoms of the myasthenic syndrome of Eaton-Lambert are weakness and aching of proximal limb muscles.[3,81] Acral paresthesias, sexual impotence and dry mouth are also common symptoms. Muscle stretch reflexes are depressed or absent in the myasthenic syndrome and muscles of ocular movement are seldom affected.[3,81] A pervasive failure of cholinergic autonomic nervous function has been described in patients with the myasthenic syndrome.[82,84]

The confirmation of the diagnosis of the myasthenic syndrome of Eaton-Lambert rests on a characteristic finding on repetitive nerve stimulation. On supramaximal stimulation of a nerve, the amplitude of the initial evoked compound muscle action potential is diminished; on repetitive stimulation at high frequencies—such as 20 to 50 Hz—there is a dramatic increment in the amplitude of the evoked response.[81,85]

Failure of neuromuscular transmission occurs in the myasthenic syndrome of Eaton-Lambert because there is an impaired release of acetylcholine from presynaptic nerve terminals despite the normal content of acetylcholine in the terminals.[86-89] There are ultrastructural alterations of neuromuscular junctions from patients with the myasthenic syndrome.[90] Freeze-fracture electron microscopy of neuromuscular junctions has shown a paucity of presynaptic active zones, structures that are important for the release of acetylcholine.[91]

The myasthenic syndrome of Eaton-Lambert may be an autoimmune disease. In one study of patients with this syndrome, 52% of the patients who did not have an associated cancer were found to have serum antibodies to thyroid, gastric parietal cell or skeletal muscle antigens.[83] In addition, the electrophysiologic and biochemical abnormalities of the myasthenic syndrome of Eaton-Lambert have been reproduced in animals by the injection of immunoglobulin obtained from patients with the syndrome.[92] Finally, treatment with immunosuppressive therapies is effective in cases of the myasthenic syndrome (see below). However, the observation that an extract of an oat cell carcinoma from a patient with the syndrome was able to produce the electrophysiologic abnormalities of the myasthenic syndrome of Eaton-Lambert in vitro also suggests that there may be more than one pathogenesis in this disorder.[93]

In patients with the myasthenic syndrome the response to treatment with acetylcholinesterase inhibitors is variable.[3,81] It may be successfully treated with the administration of guanidine hydrochloride and 4-aminopyridine, both of which increase the amount of acetylcholine released by presynaptic terminals.[3,94] These drugs do not usually render a patient completely free of symptoms and often cause serious side effects. Administering prednisone, azathioprine or both drugs in combination may be effective.[84,92,95] Plasmapheresis has also been reported to be effective.[92,95] Because most of the patients with the myasthenic syndrome of Eaton-Lambert who have improvement with immunosuppressive therapy have not had cancer, it is not clear whether patients who have both the syndrome and cancer will respond as well.

Disorders of Muscle

Three primary disorders of skeletal muscle are found in patients with cancer (Table 2). Myopathies produced by endocrinologic abnormalities associated with cancer are not included in this discussion.

Patients with inflammatory myopathy alone (polymyositis) or with cutaneous manifestations (dermatomyositis) have an incidence of cancer that has been estimated at five to seven times that of age-matched controls.[96] The reported incidence

*For a more detailed discussion of this subject, see the Specialty Conference in this issue, "Myasthenia Gravis—Current Concepts," given by Herrmann et al from UCLA.

of cancer in patients with polymyositis-dermatomyositis varies widely. Different studies have found the incidence of cancer to be between 6.7% and 34%, with an average of about 15%.[96-98] If only patients who are older than 50 years and who have polymyositis-dermatomyositis are considered, the incidence of associated cancer is about 20% in men and only slightly lower in women.[96] Perhaps dermatomyositis occurs more frequently in association with cancer than polymyositis but the significance of any observed difference is not clear.[96,97]

Polymyositis-dermatomyositis occurs in patients with a wide variety of visceral, lymphoproliferative and hematologic malignant conditions. In one study there appeared to be an overrepresentation of stomach and ovarian cancer among the patients with dermatomyositis,[98] and in another report breast cancer and stomach cancer were the most frequently noted neoplasms in patients with polymyositis-dermatomyositis.[96] The mean age of patients who have either disorder and cancer is 62 years, 15 years older than the mean age of patients with the disorders and no cancer.[96] Polymyositis-dermatomyositis is diagnosed before the appearance of cancer in 60% to 70% of the patients who have both diseases. In these patients the average interval between diagnoses is in the range of 11 to 23 months.[96,98] Cancer may appear first, however, and may precede the diagnosis of polymyositis-dermatomyositis by years.[96]

The usual clinical presentation of patients with the disorders is the subacute onset of symmetric muscular weakness that is most severe in proximal muscles. In most patients there is no muscle pain. Esophageal involvement is present in about 12% of patients and is manifest by dysphagia. Heart failure, cardiac arrhythmias and conduction disturbances are each present in less than 10% of patients with polymyositis-dermatomyositis.[96] In patients without cutaneous manifestations, this disorder may resemble several other myopathies. To improve the accuracy of the diagnosis of these disorders, diagnostic criteria have been proposed.[96] The criteria include symmetric proximal weakness, typical rash of dermatomyositis, elevation of serum muscle enzymes, characteristic abnormalities on EMG and the finding of muscle inflammation and degeneration and regeneration of muscle fibers on a muscle biopsy specimen.[96]

The biochemical evidence of muscle injury consists of elevated levels of one or more serum muscle enzymes. Creatine kinase and aldolase are the most sensitive indicators for this purpose, their levels being elevated in 95% of patients with confirmed polymyositis-dermatomyositis.[96] An abnormality of at least one serum muscle enzyme is found in 98.7% of patients. The EMG is abnormal in about 90% of patients who have polymyositis-dermatomyositis.[96] The most frequent abnormal finding on EMG is that of brief, small-amplitude muscle action potentials that are present in 90% of patients. While not specific for polymyositis-dermatomyositis, such EMG findings do show the myopathic nature of the patients' weakness. Other EMG abnormalities include increased insertional activity, positive sharp waves and fibrillation potentials.[96]

The findings on a muscle biopsy specimen are abnormal in 87.5% of patients with polymyositis-dermatomyositis. The usual pathologic abnormalities are degeneration of muscle fibers, infiltration of muscle by inflammatory cells, muscle fiber necrosis and fiber regeneration.[96] Normal results of a muscle biopsy in a patient fulfilling the other criteria for polymyositis-dermatomyositis may be due to sampling error or selecting a clinically uninvolved muscle for biopsy.

Although no placebo-controlled study of therapy has been conducted in patients with polymyositis-dermatomyositis, immunosuppression with drugs has evolved as standard treatment. About 60% to 70% of patients treated with a regimen of daily or alternate-day prednisone will experience an increase in strength and a decrease in the serum levels of muscle enzymes.[96,99,100] Adding a second drug such as azathioprine to prednisone therapy may improve the outcome of treatment and will allow maintenance of the clinical response at lower doses of prednisone.[100] Patients of advanced age and patients who have cancer, symptoms of myocarditis and weakness of long duration respond less favorably to treatment.[99] Other forms of immunosuppression such as plasmapheresis and total-body irradiation have been reported to improve the condition of patients whose disease was refractory to drug therapy.[101,102] The role that these forms of treatment will ultimately have in the management of patients with polymyositis-dermatomyositis remains to be seen.

There is a large body of evidence that indicates that this disorder is autoimmune.[103] An animal model of polymyositis—experimental allergic myositis—has been developed.[103] The experimental disease can be passively transferred by the sensitized lymphocytes of affected animals but not by serum. Studies of muscle specimens from patients with polymyositis-dermatomyositis have shown that degenerating muscle fibers are surrounded by activated T lymphocytes and macrophages.[104] Patients with active disease are more likely to have an alteration of the helper:suppressor ratio of T lymphocytes than are patients who have fully recovered.[105] The antigen against which the putative autoimmune attack is directed in polymyositis-dermatomyositis is unknown.

The pathogenesis of the myopathy in patients with carcinoid tumor appears to be different from that of the myopathy associated with other cancers. The weakness in carcinoid myopathy can be improved by treatment with the serotonin antagonists, methysergide and cyproheptadine hydrochloride,[106] suggesting that the muscle weakness in carcinoid myopathy is produced, at least in part, by the actions of serotonin.

Carcinomatous neuromyopathy is a term used to describe a syndrome of proximal muscle weakness in patients who have cancer but in whom the diagnostic criteria of polymyositis are not fulfilled and who have no other demonstrable disorder of the motor units. The findings on muscle biopsy are not specific. This diagnosis can be made in patients with cancer and proximal muscle weakness in whom polymyositis has been excluded by appropriate laboratory tests and in whom there is no evidence of a metabolic cause of muscle weakness such as the Cushing's syndrome or hypercalcemia.[107] Carcinomatous neuromyopathy resembles cachexia, a state characterized by muscular wasting and weakness, anorexia, weight loss, anemia and altered basal metabolic rate.[108] Generally, patients with carcinomatous neuromyopathy are in better general physical condition than are patients with the myopathy of cachexia. No effective treatment is known for patients with these disorders, and their causes are unknown.[108]

Conclusion

A question that must be considered at this point is what type of evaluation is indicated in attempting to find an "occult" neoplasm in a patient in whom one or more of the syndromes described here develops. Only one study has tried to answer this question in a systematic fashion.[97] The authors found that the routine use of standard diagnostic tests was not helpful in discovering asymptomatic cancer in patients with dermatomyositis-polymyositis. Anecdotal evidence culled from numerous reports of patients with neurologic paraneoplasia suggests that this is also true in patients with most of the other paraneoplastic syndromes of the nervous system. Nevertheless, recommendations can be made regarding the evaluation of patients without a known cancer in whom certain paraneoplastic syndromes of the nervous system develop.

Every patient with a paraneoplastic syndrome must undergo a thorough physical examination that should be repeated periodically. In children with myoclonic encephalopathy, two types of tests may be helpful in diagnosing an associated neuroblastoma. Urinary catecholamine levels should be measured. The finding of elevated levels of urinary catecholamines, while not sensitive enough to be considered a reliable screening test, appears to be quite specific for neuroblastoma in these children. Because about 87% of the associated neuroblastomas arise in the mediastinum or retroperitoneum,[18] it seems prudent to do a chest roentgenogram in each of these children and, if there is no evidence of tumor in the chest, a CT scan of the abdomen.

Adult patients with late-onset cerebellar degeneration, encephalomyelitis, polymyositis-dermatomyositis and the myasthenic syndrome of Eaton-Lambert should as a minimum have a chest roentgenogram because of the association between these disorders and lung cancer. Of course, patients with myasthenia gravis should be examined radiographically for the presence of a thymoma. Finally, those in whom a sensorimotor polyneuropathy develops and who have an elevated CSF protein level should be suspected of having an asymptomatic neoplasm if no other cause for such a neuropathy can be found. Chest radiography, serum and urinary protein electrophoresis and serum immunoelectrophoresis may disclose an associated lung cancer or evidence of a plasma cell dyscrasia. Some authors recommend that a radiographic skeletal survey be done in this setting because of the possibility of finding a solitary plasmacytoma.[58]

In the absence of symptoms, it seems that an exhaustive (and expensive) battery of diagnostic tests beyond those suggested above will rarely detect the "occult" cancer.

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Specialty Conference

Myasthenia Gravis—Current Concepts

Moderator
CHRISTIAN HERRMANN, Jr, MD

Discussants
JON M. LINDSTROM, PhD; JOHN C. KEESEY, MD, *and* DONALD G. MULDER, MD

An edited summary of an Interdepartmental Conference arranged by the Department of Medicine of the UCLA School of Medicine, Los Angeles. The Director of Conferences is William M. Pardridge, MD, Associate Professor of Medicine.

Current findings indicate that autoimmune myasthenia gravis is an acquired immune complex disorder of neuromuscular transmission in voluntary striated muscle. There is a break in immunologic tolerance leading to blocking and degradation of acetylcholine receptors, together with widening of the synaptic cleft associated with partial destruction, simplification and shortening of the postjunctional membrane. Thymic hyperplasia and thymoma may be present. A decremental response to nerve-muscle stimulation, blocking and jitter on single-fiber electromyography and circulating antibodies to acetylcholine receptor are detectable in most patients with generalized weakness. Although the cause of this abnormal immunologic mechanism remains to be discovered, anticholinesterases, corticosteroids, immunosuppressants, plasmapheresis or thymectomy (individually or in combination) provide control and better prognosis in most patients.

(Herrmann C Jr, Lindstrom JM, Keesey JC, et al: Myasthenia gravis—Current concepts—Interdepartmental Conference, University of California, Los Angeles [Specialty Conference]. West J Med 1985 Jun; 142:797-809)

CHRISTIAN HERRMANN, JR, MD:* Thomas Willis in 1672 is credited with the early description of what we now know as myasthenia gravis:

> Nevertheless, those laboring with a want of Spirits, who will exercise local motions, as well as they can, in the morning are able to walk firmly, to fling about the Arms hither and thither, or to take up any heavy thing; before noon the stock of the Spirits being spent, which had flowed into the Muscles, they are scarce able to move Hand or Foot. At this time I have under my charge a prudent and an honest woman, who for many years hath been obnoxious to this sort of spurious Palsie, not only in her Members, but also in her tongue; she for some time can speak freely and readily enough, but after she has spoke long, or hastily, or eagerly, she is not able to speak a word, but becomes as mute as a Fish, nor can she recover the use of her voice under an hour or two.[1]

Samuel Wilks in 1877 gave the next comprehensive classical case report of a young woman who had variable generalized weakness, diagnosed as hysteria by the house officer, and oropharyngeal and respiratory muscle weakness later developed. Because no effective treatment was available at that time, she died. At autopsy the first microscopic examination of the central nervous system in such a case showed no abnormalities.[2]

The German pathologist Carl Weigert[3] reported the association of thymoma with myasthenia in 1901. The association of thymic hyperplasia with lymphoid germinal centers was described in 1943.[4] Embryologically, the thymus derives from the third branchial cleft and descends from just below the thyroid in the neck into the chest. It is a paired structure with the greatest bulk of the gland usually located in the left lobe in the anterior superior mediastinum, with slender poles extending downward from the neck. It may be located anywhere from the neck to the diaphragm in the anterior mediastinum. In 1911 Sauerbruch and co-workers[5] removed the thymus from a young woman with hyperthyroidism and myasthenia gravis. The myasthenia abated but the hyperthyroidism required thyroidectomy.

In 1932 Loewi[6] showed that acetylcholine transmitted the nerve impulse in the heart, and in 1936 Sir Henry Dale[7] identified this as the transmitter to striated muscle, which was terminated by the action of cholinesterase.

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Because of the lack of effective treatment, 85% of patients died within the first two years of the onset of myasthenia. But in 1934, Mary Walker, a house officer at St Alfege's Hospital in London, was caring for patients with myasthenia. Being aware of the similarity between the symptoms and signs of myasthenia gravis and curare poisoning, and the fact that physostigmine was an antidote for the latter, she tried this on her patients; some improved but undesirable side effects also occurred. She learned of a synthetic analogue of physostigmine, neostigmine (Prostigmin), with fewer side effects, which she used more effectively. However, she also noted that anticholinesterase drugs, while effective in some areas, often failed to relieve all symptoms and signs of myasthenia, a feature still found today.[8]

After Walker showed the benefits of the use of neostigmine in England, Viets, a Boston neurologist, had his intern inject it into a patient with myasthenia gravis for the first time at Massachusetts General Hospital (Boston) in 1935.[9] The same year Lindsley, a physiologic psychologist at Harvard, studied patients with myasthenia gravis at the Massachusetts General Hospital. He showed a decline in the effectiveness of muscle contraction and variable amplitude of the motor unit action potential.[10]

A clinical feature of myasthenia gravis is intermittent weakness of voluntary muscles that increases with use and is relieved, at least in part, after a short rest. Extraocular, facial, oropharyngeal, nuchal, respiratory and limb muscles are often involved. Common symptoms are drooping of the eyelids, double vision, the loss of facial expression, fatigued and indistinct voice, weakness in chewing and swallowing, weakness of the neck with difficulty elevating and holding the head erect, weakness of the limbs with fatigability and at times increasing difficulty in breathing.

Table 1 lists the common initial symptoms in the first 177 patients seen at UCLA by 1963. Some time often elapsed from onset before we saw and examined these patients; the areas in which we detected weakness on clinical neurologic examination are also presented in Table 1.[11]

Myasthenia gravis is seen in all races and in both sexes at any age. In two thirds of women it develops before the age of 40 and in two thirds of men after 40.[12] Although it is considered a "rare disease" with an estimated incidence of from 1:10,000 to 1:40,000 of the population, we have seen 849 patients at UCLA in 29 years; two thirds were women and one third men.

The disorder appears transiently and lasts for days to weeks in 12% of infants born to mothers with myasthenia gravis.[13] This is termed transient neonatal myasthenia as opposed to congenital myasthenia in which the mother does not have myasthenia gravis and evidence for an autoimmune process is absent.[14] Several less common disorders of neuromuscular transmission resemble myasthenia gravis but these do not have antibody to acetylcholine receptor or thymic abnormalities. This presentation is limited to autoimmune myasthenia gravis.

At times the weakness becomes so severe that it interferes with a patient's ability to maintain airways free of secretion or adequate respiratory exchange or both. This is called crisis.[15] It may result from worsening of the myasthenic process, a toxic effect of therapy or both. Often both factors are operating and to distinguish between them rapidly is difficult. It is best to control the airways quickly and ventilate the patient. One may then deliberate about the cause of the crisis.

The rapid-onset and short-acting anticholinesterase, edrophonium chloride (Tensilon), is useful for diagnostic testing.[16] Unlike the intermediate-acting anticholinesterase drugs, it may have some direct stimulatory action on muscle but, like other anticholinesterase drugs, it may not relieve all symptoms and signs. Failure to respond to Tensilon, while not favoring the diagnosis of myasthenia gravis, does not exclude it. Pyridostigmine bromide (Mestinon) acts slightly longer than neostigmine, often with fewer cholinergic side effects.[17] Currently, it is the most frequently used anticholinesterase drug for treating myasthenia. Ambenonium chloride (Mytelase) is another intermediate-acting anticholinesterase but it has a relatively narrow margin between therapeutic and toxic dose.[18]

In the absence of an animal model, the introduction in 1957 by Dillon and Sabawala[19] of in vitro intercostal muscle biopsy of patients with myasthenia gravis at the University of California, Los Angeles (UCLA), aided in the pharmacologic study. The intercostal muscle is convenient to study in the laboratory; it is short, with its origin on one rib and insertion on the next. A neuromuscular junction is always present between these two points. This junction may be studied conveniently for several hours in a heated oxygenated perfusion bath.[20,21] It has since been used for microelectrode, electrophysiologic, histochemical, immunohistochemical and electron-microscopic study elsewhere to elucidate the abnormalities of neuromuscular transmission in myasthenia and other disorders.

The concept of a possible curarelike substance in the

TABLE 1.—*Common First Symptoms and Signs of Muscle Weakness at Subsequent Neurologic Examination in Patients With Myasthenia Gravis**

	Percentage
Symptoms	
Drooping lid(s)	25
Double vision	41
Trouble with voice	16
Trouble swallowing	10
Trouble chewing	7
Weak arms and/or hands	7
Weak legs	13
General weakness	11
Signs of Muscle Weakness	
Eyelid levator	58
Extraocular muscles	54
Jaw	32
Eyelid closers	71
Face	63
Swallowing	24
Speech	33
Tongue	33
Neck	61
Shoulder and arm	72
Hand and finger	68
Leg	75
General	11

*Based on 177 patients with myasthenia gravis—102 women and 75 men—seen in the Myasthenia Gravis Clinic at UCLA by the author (C.H.). Some patients had more than one initial symptom.

serum of patients with myasthenia was pursued by investigators. In 1959 Nastuk and Strauss[22] found a heat-labile cytolytic agent when myasthenic serum was applied to the sartorius muscle of a frog. The worsening of myasthenia with infection was a well-known phenomenon. Also in 1956, Nastuk and associates[23] noted a fall in serum complement in patients with myasthenia who were getting worse, particularly those in crisis. The question of an immunologic mechanism was raised. In 1960 Simpson, a neurologist in Edinburgh, after reviewing a large series of patients with myasthenia in England, noted the association with other disorders thought to be on an autoimmune basis and proposed this for myasthenia.[24] Strauss and colleagues during the same year showed a striated muscle-binding, complement-fixing serum globulin in 30% to 50% of patients with myasthenia.[25] Table 2 lists disorders (several of which have an autoimmune basis) associated with myasthenia gravis.[26(pp 27-30)]

In 1966 van de Velde and Friedman, aware that Mayer had described myoid cells in the thymus of lower animals in 1888, looked for these and found them in the thymoma of a male patient.[27] Could these be the built-in source of antigen for striated muscle antibodies and acetylcholine-receptor antibodies to be discovered later? Serum autoantibodies seen in patients with myasthenia gravis are shown in Table 3.[26(pp 110-132)]

As more patients were seen, the presence of myasthenia gravis in more than one member of a family was noted in siblings or parent and child. Although myasthenia is not inherited by dominant, recessive or sex-linked mechanisms, it was found more frequently in certain families than in the general population.[28] Further studies of monozygotic twins showed nonconcordance in the dizygotic twins and concordance in only 40% of the monozygotic twins.[26(pp 40-41)] This suggested the presence of a susceptibility or predisposition of a genetic sort with an exogenous factor setting off the mechanism. With the availability of human leukocyte antigen typing, the association of myasthenia gravis with D8 and D3 was reported and confirmed.[29]

TABLE 2.—*Disorders Associated With Myasthenia Gravis*

Thymic hyperplasia	Vitiligo
Thymoma	Pemphigus
Invasive or malignant thymoma	Multiple sclerosis
Hyperthyroidism (Graves')	Sarcoidosis
Hypothyroidism	Ulcerative colitis
Thyroiditis (Hashimoto's)	Leukemia
Rheumatoid arthritis	Lymphoma
Systemic lupus erythematosus	Convulsive disorder
Hemolytic anemia	Polymyositis
Pernicious anemia	Scleroderma
Red cell aplasia	Sjögren's syndrome
Idiopathic thrombocytopenic purpura	

TABLE 3.—*Serum Antibodies Associated With Myasthenia Gravis*

Acetylcholine receptor	Smooth muscle
Striated muscle	Heterophile
Thyroglobulin	Platelet
Thyroid microsomal	Lupus erythematosus preparation
Antinuclear	False-positive serology
Gastric parietal cell	Coombs' test
Mitochondrial	Epithelial cell
Rheumatoid factor	Basement membrane
Lymphocyte	

As might be expected in an autoimmune disorder, the effectiveness of adrenocorticotropic hormone was established in 1966 by von Reis and co-workers.[30] The effectiveness of corticosteroids was shown by Engel and Warmolts in 1971.[31]

In 1973 Patrick and Lindstrom introduced an animal experimental model of myasthenia gravis by injecting the electric organ of eel with Freund's adjuvant into rabbit.[32] Decrementing muscle action potentials were shown with repetitive nerve-muscle stimulation and strength was improved with the administration of neostigmine. Antibody to acetylcholine receptor was detected in the serum of the immunized animals. Subsequently, antibody to acetylcholine receptor was detected in the serum of patients with myasthenia and techniques were developed to measure this as a useful diagnostic aid.

Using electrophysiologic, immunohistochemical and electron-microscopic techniques, Engel and associates showed in 1977 and 1981 the presence of immune complexes of IgG, C3 and C9 at the motor end-plate in myasthenia gravis.[33,34] In 1971 Engel and Santa had shown widening of the synaptic cleft, along with shortening and destruction of the postjunctional membrane, in myasthenia gravis.[21]

Unfortunately, the titer of acetylcholine-receptor antibody did not correlate well with the clinical severity and course in a patient.[35] In an attempt to explain how the autoimmune complex process may be altering neuromuscular transmission at the junction, Drachman and colleagues in 1982 studied the ability of the serum immunoglobulin from patients with myasthenia to induce accelerated degradation or blockade of the binding sites of acetylcholine receptors.[36] They found a high correlation of the combined activity of the immunoglobulin in accelerating degradation and producing blockade in relation to the clinical state of a patient.[36] The ability of these mechanisms in reducing the number of available acetylcholine receptors was pertinent to the clinical pathogenesis in myasthenia.

Various measures used recently to treat myasthenia are listed in Table 4.[26(pp 184-238)] The major forms and their effects will be presented by the other participants.

The Acetylcholine Receptor and Experimental Autoimmune Myasthenia Gravis

JON M. LINDSTROM, PHD:* The muscular weakness characteristic of myasthenia gravis is caused by an autoimmune response to acetylcholine receptors at neuromuscular junctions. A decade ago it was shown that immunizing rabbits with acetylcholine receptors purified from the electric organs of electric eels provoked the formation of antireceptor antibodies that cross-reacted with receptors in rabbit muscles and caused muscular weakness and excessive fatigability.[32,37] Since then, myasthenia gravis was shown to involve an autoimmune response to acetylcholine receptors; the pathologic mechanisms by which antibodies to receptor impair neuromuscular transmission in both myasthenia gravis and experimental autoimmune myasthenia gravis have been

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characterized in detail and extensively reviewed.[38-41] These studies have provided new approaches to the diagnosis of myasthenia gravis (for example, by radioimmunoassay) and treatment of myasthenia gravis (for example, by plasmapheresis and immunosuppressive drugs). Experimental autoimmune myasthenia gravis is now also being used to investigate approaches to specific suppression of the immune response to receptor. Recent advances using monoclonal antibodies and genetic engineering have made it possible to study acetylcholine receptors and the autoimmune response to these receptors at a more precise molecular level than ever before. The structure and function of acetylcholine receptors[42-46] and the use of monoclonal antibodies to study receptors and experimental autoimmune myasthenia gravis[47-50] have recently been extensively reviewed. All of these topics will be briefly reviewed here.

Binding of acetylcholine released from the nerve endings to receptors in the postsynaptic membrane of the muscle triggers the opening of a cation-specific channel through which cations passively flow, causing a depolarization of the postsynaptic membrane. If a sufficient number of receptors are activated, the depolarization will trigger an action potential in the muscle, thereby completing neuromuscular transmission. In myasthenia gravis and experimental autoimmune myasthenia gravis, the number of functional receptors is reduced, and neuromuscular transmission is often unsuccessful, especially after repeated nerve impulses.

TABLE 4.—*Various Forms of Treatment of Myasthenia Gravis*

- Cholinesterase inhibitors
  - Neostigmine bromide and methylsulfate (Prostigmin)
  - Edrophonium chloride (Tensilon)
  - Pyridostigmine bromide (Mestinon)
  - Ambenonium chloride (Mytelase)
- Adrenocorticotropic hormone
- Corticosteroids
- Cytotoxic drugs
  - Azathioprine
  - Cyclophosphamide
  - Methotrexate
  - 6-Mercaptopurine
- Thoracic duct drainage
- γ-Globulin
- Antilymphocytic and antithymocytic globulin
- Plasma exchange
- Thymectomy (transsternal and transcervical)
- Miscellaneous agents
  - Ephedrine
  - Potassium
  - *Veratrum* alkaloids (germine mono- and diacetate)
  - Xanthine derivatives
    - Aminophylline
    - Oxtriphylline
    - Guanidine hydrochloride
    - 4-Aminopyridine
- Irradiation
  - Mediastinal (thymic)
  - Splenic
  - General

The acetylcholine receptor (Figure 1) contains two acetylcholine binding sites and the cation channel whose opening they regulate.[42-46] The receptor is formed by four kinds of glycoprotein subunits in the ratio $\alpha_2\beta\,\gamma\,\delta$.[52-54] The acetylcholine binding sites are on the α-subunits.[45] The cation channel across the membrane is thought to be formed by part of each subunit organized like the staves of a barrel around a central channel.[46]

The complementary DNAs for each of the subunits of receptor from *Torpedo* electric organ have been cloned and sequenced.[55-60] The protein subunits have the following molecular weights: α, 50,116; β, 53,681; γ, 56,601, and δ, 57,565, giving the complete receptor a protein molecular weight of 268,079.[55,56] The amino-acid sequences of the subunits are highly homologous throughout their lengths.[54,56,61] This means that they evolved through duplication and reduplication of a primordial gene. It also means that the fundamental shape of each subunit is similar. The best current evidence suggests that each subunit has four transmembranous hydrophobic α-helical domains[56,58,61] and a fifth transmembranous amphipathic α-helical domain, which is the part of each subunit that forms the hydrophilic lining of the channel.[46,62] The receptor is about 11-nm long in the axis perpendicular to the membrane with about 5.5-nm extending on the extracellular surface of the membrane and 1.5-nm extending on the cytoplasmic surface.[51] A complete cDNA for the α-subunit of human acetylcholine receptors has been cloned and sequenced.[57] The α-subunit of receptor from human muscle has 80% sequence homology with the α-subunit of receptor from *Torpedo* electric organ. Thus, the structure of receptor from *Torpedo* electric organ is a good model for the structure of receptor from human muscle. Purified receptor can be reconstituted into model membrane vesicles[63,64] and into lipid bilayers in which the opening and closing of single channels can

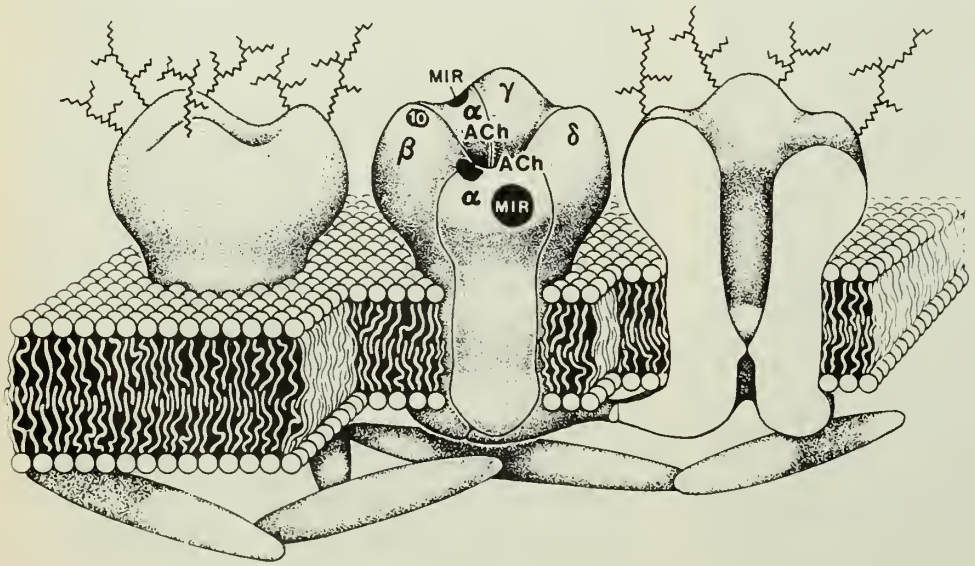

Figure 1.—Acetylcholine-receptor structure. This cartoon is based largely on structural models of the receptor proposed by Kistler and co-workers[51] in which the 2 α- and the β-, γ- and δ-subunits are organized like barrel staves around a cation channel through the center of the molecule. The acetylcholine binding sites **(ACh)** and the main immunogenic region **(MIR)** are located on the extracellular surface of α-subunits. Sugars on the extracellular surface of the subunits are indicated by branched chains. Extrinsic membrane proteins associated with the cytoplasmic surface of the receptor such as the "43,000 molecular weight protein" are suggested by cigar-shaped structures on the cytoplasmic surface. (Modified from Anholt and associates.[42])

be monitored electrophysiologically.[65-68] The functional properties of reconstituted purified receptors from *Torpedo* electric organ are quite similar to those of receptors in muscle.

The antigenic structure of acetylcholine receptors has been determined primarily using monoclonal antibodies.[47-50] When intact acetylcholine receptors are used as immunogen, about half of the antibodies made are directed at a small part of the extracellular surface of the α-subunits referred to as the "main immunogenic region."[69-71] The immunogenicity of this region depends largely on its native conformation. The acetylcholine binding sites form a small part of the surface of the receptor and only a small fraction of antireceptor antibodies bind at, or near, the acetylcholine binding sites.[37,72] The individual denatured subunits are much less immunogenic than is the intact receptor,[73,74] and most of the antibodies made are directed at the cytoplasmic surfaces of the subunits.[75,76] Monoclonal antibodies to the main immunogenic region[50,77] and most serum antibodies that can bind to receptors in intact cells[78] have little or no effect on receptor function.

The specificities of antireceptor autoantibodies in the serum of patients with myasthenia gravis have been studied using monoclonal antibodies (Figure 2).[81] We determined the fraction of autoantibodies inhibited from binding to receptor from human muscle by rat monoclonal antibodies directed at various parts of the receptor. We found that about half of the autoantibodies were directed at the main immunogenic region, but that significant amounts were directed at β- and δ-subunits. This means that the spectrum of antireceptor antibodies in patients with myasthenia gravis is similar to that in rats with experimental autoimmune myasthenia gravis—that is, antibodies are directed at many parts of the receptor molecule but preferentially the main immunogenic region. Individual patients with myasthenia gravis differed somewhat in the spectrum of antireceptor specificities they produced, but this did not vary with time or clinical state. On the average, patients in all clinical states had the same basic spectrum of antireceptor antibodies.

The fundamental lesion in experimental autoimmune myasthenia gravis[80,81] and myasthenia gravis,[82-84] which impairs neuromuscular transmission, is the loss of acetylcholine receptors. One mechanism by which receptors are lost is complement-mediated focal lysis.[84-86] Complement-mediated focal lysis is probably responsible for the simplification of the normally folded structure of the postsynaptic membrane that characterizes both chronic experimental autoimmune myasthenia gravis and myasthenia gravis.[21,87]

Another mechanism of receptor loss is antigenic modulation.[78,88-90] Antigenic modulation is an increase in the normal rate of receptor destruction caused by crosslinking of receptors by antibodies, which facilitates their endocytosis and lysosomal destruction. Experimental autoimmune myasthenia gravis can be passively transferred with antiserum[81] and monoclonal antibodies.[69,91,92] In rats, passive transfer is associated with complement fixation[93] and an influx of macrophages that destroy the postsynaptic membrane.[87] Such a phagocytic invasion is not seen in cases of chronic experimental autoimmune myasthenia gravis or in myasthenia gravis where the rates of increase in antireceptor antibody concentration are much slower than in animals injected with antibody.

Antibodies to the main immunogenic region can passively transfer experimental autoimmune myasthenia gravis.[69] Antibodies to the main immunogenic region can crosslink receptors into aggregates because there are two α-subunits per receptor and because the main immunogenic region on each α-subunit is oriented in such a way that the two regions on a single receptor cannot be crosslinked by a single antibody.[94] Because antibodies to the main immunogenic region can crosslink receptors, they can cause antigenic modulation of receptors.[94] Thus, the most frequent specificity of antireceptor antibody in both experimental autoimmune myasthenia gravis and myasthenia gravis is capable of both of the patho-

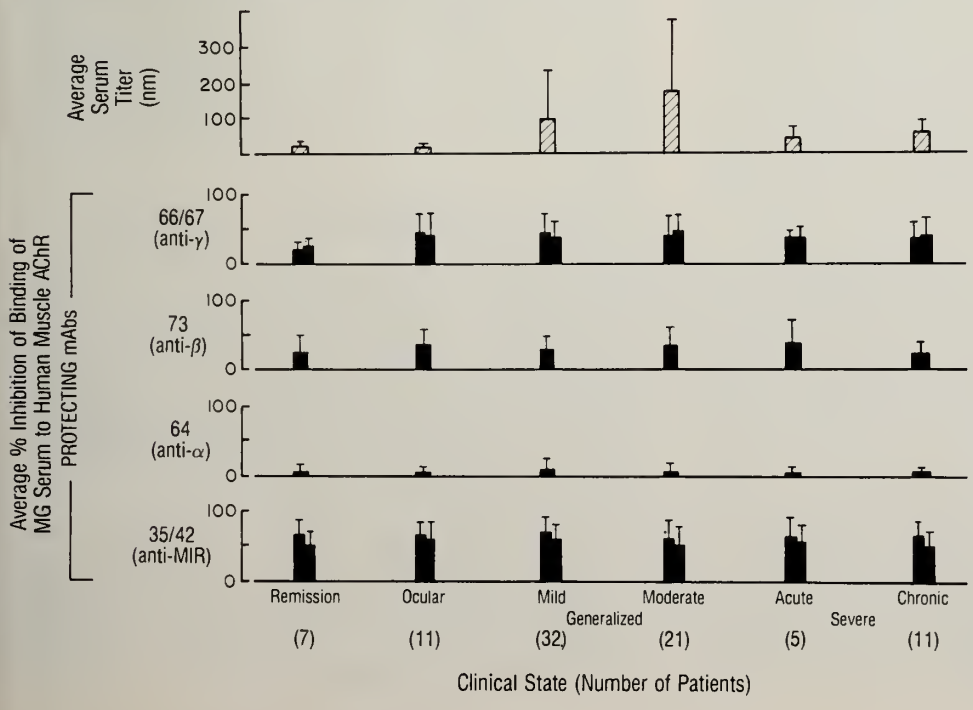

Figure 2.—Relation between the clinical state of patients with myasthenia gravis (MG) and the spectrum of antireceptor autoantibodies they produce. In all clinical states the average spectrum of autoantibody specificities is the same, with antibodies to the main immunogenic region predominating. (From Tzartos et al.[79]) mAbs = monoclonal antibodies, AChR = acetylcholine receptor, MIR = main immunogenic region

logic mechanisms that cause loss of receptor and, thereby, impairment of neuromuscular transmission.

Although the symptoms of myasthenia gravis can be partially controlled by using inhibitors of anticholinesterase to increase the duration and concentration of acetylcholine and thereby partially compensate for the loss of acetylcholine receptors, and although thymectomy, various immunosuppressive drugs and plasmapheresis can be beneficial, there is no specific cure for myasthenia gravis. The idea of taking advantage of the extensive molecule information about acetylcholine-receptor structure and the availability of experimental autoimmune myasthenia gravis as an animal model of myasthenia gravis to study specific immunosuppression is appealing. Although experimental autoimmune myasthenia gravis is an excellent model for studying the pathologic mechanisms by which an immune response to receptor impairs neuromuscular transmission, experimental autoimmune myasthenia gravis does not show the (unknown) mechanisms by which the immune response to receptor in myasthenia gravis is initiated and sustained.

Christadoss and co-workers showed that a primary reason why various mouse strains differed in their susceptibility to induction of experimental autoimmune myasthenia gravis was genetic differences in their Ia determinants.[95] Ia molecules are involved in antigen recognition by macrophages and B cells. Waldor and associates have reported that a monoclonal antibody to Ia can reduce the immune response to receptor in inbred mice.[96] The practicality of such an approach to myasthenia gravis remains to be established.

That antibodies to the main immunogenic region predominate and are abnormally significant in both experimental autoimmune myasthenia gravis and myasthenia gravis might suggest that anti-idiotypic therapy would be beneficial. Lennon and Lambert showed, however, that raising anti-idiotype antibodies to rat monoclonal antibodies that could passively transfer experimental autoimmune myasthenia gravis did not protect these rats from the subsequent induction of experimental autoimmune myasthenia gravis by immunization with receptor.[91] Similarly, we found that even though conjugation of a monoclonal antibody to the main immunogenic region with bacterial lipopolysaccharide permitted inducing high levels of anti-idiotype antibody in rats, they were not protected from induction of experimental autoimmune myasthenia gravis.[97] We also found that there was very little cross-reaction between this anti-idiotype serum and other monoclonal antibodies to the main immunogenic region. Thus, antigenic specificity is not the same as idiotypic specificity. This is not surprising because even a simple hapten can provoke antibodies of several idiotypes in inbred mice,[98] so a determinant composed of at least eight or ten amino acids in a specific conformation should provoke antibodies of many idiotypes. Anti-idiotype approaches to specific immunosuppression would be even less likely to succeed in an outbred human population.

Another approach that we have been investigating is the use of conjugates of ricin toxin with receptor to kill specifically receptor-sensitive lymphocytes. Many laboratories have been coupling toxins like ricin, which enzymatically inhibit protein synthesis, with hormones, or antibodies, to form magic bullets to kill specifically cell-bearing hormone receptors, or specific antigens.[98-104] The bound toxins are endocytosed along with their target during normal turnover of the target and enter the cytoplasm through the lysosomal membrane. Ricin is derived from castor beans and consists of a toxic subunit joined to a sugar-binding subunit by a disulfide bond. To avoid nonspecific killing, the sugar-binding subunit must be removed or specifically inhibited. The toxin-conjugate "magic bullets" have been successfully used in some in vitro experiments. We have obtained encouraging results using such conjugates to suppress receptor-induced proliferation of T lymphocytes and receptor-induced production of antireceptor antibodies by B lymphocytes in cell cultures from rats with experimental autoimmune myasthenia gravis.[105] These studies are still well away from in vivo studies for the prevention and treatment of experimental autoimmune myasthenia gravis and still further removed from practical application to patients with myasthenia gravis.

There are several other approaches to specific suppression of the immune response to receptor. For example, suppressor factors produced by T-cell lines or T-cell hybridomas are being investigated in several laboratories. In animals with experimentally induced allergic encephalomyelitis, Kardys and Hashim[106] have reported that altering a single amino acid in an encephalitic peptide synthesized to correspond to a myelin basic protein sequence causes the resulting peptide not to be encephalitogenic and to protect rats from immunization with the encephalitogenic peptide.[106] When the peptide sequence and conformation corresponding to the main immunogenic region can be identified, similar manipulation of experimental autoimmune myasthenia gravis may be undertaken.

To conclude, molecular studies of acetylcholine receptors intertwined with immunologic studies of experimental autoimmune myasthenia gravis and myasthenia gravis have shown the autoimmune nature of myasthenia gravis and provided a molecular perspective on many aspects of the pathologic mechanisms by which neuromuscular transmission is impaired. These studies have improved the diagnosis and treatment of myasthenia gravis. However, many aspects of the pathologic mechanisms remain unexplained at a molecular level. Discovering how the autoimmune response to receptor is initiated and sustained in myasthenia gravis and discovering methods for specifically inhibiting this autoimmune response present interesting challenges for further research.

Clinical Electrophysiology and Immunology of Myasthenia Gravis

JOHN C. KEESEY, MD:* The clinical hallmark of myasthenia gravis is fluctuating specific skeletal muscle weakness made worse by repeated use and relieved, at least partially, by rest. The diagnosis is easy to make clinically in obvious cases, but in patients in whom weakness is mild or restricted to only a few muscles, the presence of myasthenia may be questioned. Clinicians, therefore, turn to electrophysiologic and immunologic testing to confirm their clinical impression.

Laboratory Testing for Myasthenia

Repetitive nerve stimulation. Repetitive nerve stimulation testing has been used for more than 40 years to show

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defects of neuromuscular transmission in humans.[107] When electrical stimulation is applied to the skin overlying the motor nerve to a muscle, a compound muscle action potential may be recorded. The compound muscle action potential is usually made up of electrical contributions from all the individual muscle fibers in the muscle underlying the recording site, if all the nerve fibers to that muscle are stimulated by a supramaximal stimulus. In diseases of neuromuscular transmission such as myasthenia gravis, as more and more individual neuromuscular junctions fail to transmit the nerve impulse to the muscle fiber with repeated stimulation, the size of consecutive compound muscle action potentials decreases, especially at stimulation rates of two to three per second.

In practice, recordings have been made most often over small muscles in the hand to minimize movement artifacts and patient discomfort. Unfortunately for diagnostic purposes, only 43% of patients with clinically accepted myasthenia gravis show a decremental response of the small hand muscles at rest.[108] Various techniques have been suggested to decrease the number of these false-negatives, including increasing the temperature of the muscle by warming the extremity,[109] recording muscles that have been previously stimulated either electrically or during voluntary exercise to check for "posttetanic exhaustion,"[110] recording muscles rendered ischemic by a tourniquet[111] and using more proximal muscles.[112] Even with these more difficult and often unpleasant additions, some patients who definitely have myasthenia gravis clinically still fail to show abnormal responses on repetitive nerve stimulation testing.

Single-fiber electromyography. One of the reasons that repetitive nerve stimulation testing does not detect all neuromuscular transmission defects in many patients with myasthenia gravis is that the test requires complete transmission blockade in many neuromuscular junctions before the compound muscle action potential begins to show a measurable decrement. Before complete blockade, however, failing neuromuscular transmission shows increasing delay reaching the threshold for muscle activation. This delay can be detected using a needle electrode with a small 25-micron surface, capable of recording the electrical activity of single muscle fibers.[113] Once a pair of single muscle fibers innervated by the same nerve is located electrically by the electrode during gentle voluntary contraction, the variation in the time interval between the two action potentials during successive impulses can be measured. This is called the neuromuscular jitter,[113] and it is increased significantly in disorders of the neuromuscular junction, including myasthenia gravis.[114] Complete blockade of neuromuscular transmission in one of the pair of fibers can also be detected and is usually found in pairs showing the most jitter. This test is quite time-consuming and requires considerable skill.

The data from two studies comparing the sensitivity of repetitive nerve stimulation and single-fiber electromyography[114,115] are presented in Table 5 in terms of the percentage of patients—especially those with mild myasthenia or myasthenia limited to the ocular muscles—who have normal results with each test ("false-negatives"). Single-fiber electromyography is more sensitive in each category than repetitive nerve stimulation. However, there are a few patients with mild myasthenia (4% to 8%) and a few with ocular myasthenia (23% to 40%) who are still not detected by single-fiber electromyography, perhaps because the muscle tested (usually the extensor digitorum) is not involved in the disease process.

Serum acetylcholine-receptor antibodies. The clinical electrophysiologic tests described above look for overall dysfunction at the neuromuscular junction and as such are nonspecific, showing decremental responses or increased jitter in many conditions other than myasthenia gravis, as well as in myasthenia from whatever cause. The serum acetylcholine-receptor antibody titer, on the other hand, is very specific for the diagnosis of autoimmune myasthenia gravis.[116] It is therefore particularly useful when it is elevated because it permits a rational basis for proceeding with therapies based on immunosuppression or removal of the thymus.

However, the serum acetylcholine-receptor antibody titer (measured by the radioimmunoprecipitation method with human muscle as antigen) is normal in 12% to 24% of cases of spontaneous adult myasthenia (Table 5), in 24% to 30% of those of ocular myasthenia (Table 5) and in all cases of presumably nonautoimmune congenital myasthenia. The correlation of antibody titer with clinical course is unpredictable in individual patients and, in groups of patients classified by disease severity, the statistical correlation is not dramatic.[117]

The above laboratory testing is unable to confirm the diagnosis in every patient in whom the clinical history and results of a physical examination suggest the diagnosis of myasthenia gravis. Perhaps more complete confirmation could be obtained by combining these tests with curare provocation[118] or motor-point muscle biopsy for acetylcholine-receptor measurement.[119] However, on some occasions the clinical im-

TABLE 5.—*Results of Laboratory Testing for Myasthenia Gravis*

Procedure	False-Positives	False-Negatives: Definite Myasthenia Percent	False-Negatives: Mild Myasthenia Percent	False-Negatives: Ocular Myasthenia Percent	False-Negatives: Myasthenia in "Remission"* Percent	References
Single-fiber electromyography						
Forearm (extensor digitorum communis)	Yes	0	4-8	23-40	31-40	Stalberg and Sanders,[114] Kelly et al[115]
Frontalis	Yes	...	...	15	...	Stalberg and Sanders[114]
Serum antibody to human acetylcholine receptor	No	12	20-24	24-30	40	Stalberg and Sanders,[114] Kelly et al[115]
Repetitive nerve stimulation						
Shoulder	Yes	11	32	81	100	Stalberg and Sanders[114]
Hand	Yes	32	69	96	100	Stalberg and Sanders[114]

*Remissions were steroid-dependent in reference 8.

pression alone, if strong enough, must be the sole basis for beginning therapy for myasthenia gravis.

Detection of Thymoma

Chest radiography. A lymphoepithelial thymoma occurs in as much as 15% of adult patients with myasthenia gravis.[120] Once the diagnosis of myasthenia gravis is made in a particular patient, the next clinical question is whether or not a thymoma is present. Because the presence of a thymoma would favor surgical thymectomy as the treatment of choice for that patient,[121] various tests have been evaluated for their ability to detect the presence of thymoma. Routine chest radiography alone missed 23% to 50% of surgically and histologically proved thymomas.[122-124]

Mediastinal tomography. Conventional linear tomography missed 9% to 33% of proved thymomas.[123,124] Computed tomography (CT) detected all thymomas in several studies, but it was also similarly abnormal in 33% to 86% of patients with myasthenia proved not to have thymomas.[123,124] A normal thymus in younger patients (under 40 years of age) may produce an anterior mediastinal density on CT scan that is indistinguishable from thymoma. Although a calcified anterior mass on CT is "undoubtedly" a thymoma,[124] a normal CT scan does not rule out the presence of thymoma.[125]

Serum striated muscle antibody. Of patients with myasthenia gravis who also have a thymoma, 95% to 100% were found to have elevated titers of serum antibodies to striated muscle.[126-128] In addition, 30% of patients with myasthenia without thymoma[127] and 24% of patients with only thymoma[128] had these antibodies. If negative, however, this serologic test is strong but not absolute evidence against the presence of a thymoma in a patient with myasthenia gravis.[123]

As with the diagnosis of myasthenia discussed above, a clinician must sometimes disregard the normal laboratory values in determining the best treatment for a patient. Recently a 47-year-old woman who had had a few months of rapidly progressive myasthenia gravis, with a prominently elevated serum acetylcholine-receptor antibody titer, underwent elective thymectomy at UCLA as treatment for her myasthenia. Both her CT scan and her striated muscle antibody titer were normal, so it came as a surprise to discover at operation that a thymoma in the left lobe of the thymus was invading the medial surface of the left lung and the pericardium and was encasing the left phrenic nerve. Patients with myasthenia gravis treated pharmacologically for many years before the eventual radiologic discovery of the presence of a thymoma are relatively common. Clinicians, therefore, may decide to recommend thymectomy for individual middle-aged or even elderly patients with myasthenia gravis for whom the radiologic and serologic tests do not indicate the presence of a thymoma.

Immunologic Therapies

A heading of "Immunologic Therapies" implies that the mechanism of therapeutic effectiveness for the following agents is actually known, which is not the case. For instance, steroids and azathioprine have been shown to have direct stimulatory effects on neuromuscular transmission, in addition to their accepted actions as immunosuppressants.[129,130]

Glucocorticosteroids. An early effect of glucocorticosteroids unique to myasthenia gravis is that patients may become much weaker when first placed on a therapeutic regimen of glucocorticosteroids. This may be life-threatening if respiratory or bulbar symptoms are prominent, and therefore the use of these agents was formerly cautioned against in the treatment of myasthenia gravis.[131] Glucocorticosteroids have now become a standard treatment for myasthenia gravis, however,[132] although there is still controversy about the best method of administration.[133]

One school, which firmly believes that any form of steroid therapy should begin with an intensive course,[134] recommends 60 to 80 mg of prednisone given daily along with anticholinesterase as the initial form of therapy until improvement begins, usually within four weeks.[135] Their recommendations are based on a published series of 60 patients with myasthenia.[136] Some degree of worsening occurred in about half of these patients 1 to 21 days after beginning prednisone therapy and lasted an average of six days. Patients were therefore placed under inpatient observation during the first two to three weeks of intensive prednisone therapy. Most patients reached a pronounced degree of improvement within six to eight weeks, although maximum response occurred after about five months of daily high-dose prednisone therapy. Of severely affected patients, 29% had a drug-dependent remission and another 53% showed substantial improvement.[135] There was a 25% incidence of serious complications from daily steroid therapy, including cataracts, sepsis, vertebral collapse, gastrointestinal hemorrhage, diabetes mellitus, pneumonia, pulmonary embolism and three deaths.

In an attempt to lessen side effects, patients were gradually converted to alternate-day therapy (100 to 120 mg given every other day) after about two months of daily therapy. Then, after 3 to 12 months of receiving high doses of prednisone on alternate days, an attempt was made to taper the prednisone dose very gradually (5 mg per month) without an exacerbation of muscle weakness. Below 50 mg every other day, tapering was at a rate of 2.5 mg per month and tapering was not pursued beyond 5 to 10 mg of prednisone on alternate days. Administration of that dose indefinitely was recommended.[134] Improvement was not maintained if prednisone therapy was discontinued, unless natural remission or some other mode of therapy, such as thymectomy, intervened. More than half of the patients had elective thymectomy while taking prednisone.

To lessen, but not completely avoid, the initial worsening of myasthenia and the necessity for close inpatient observation with intensive courses of prednisone, an alternative drug regimen has been proposed on the basis of 12 successful cases,[137] a regimen in which the dose of prednisone is gradually increased. Indications for prednisone therapy included generalized myasthenia gravis with significant disability, older patients (more than 50 years) and patients with thymoma.[138,139] Although there is not a fixed schedule, the suggested regimen most widely adopted[138] has been to begin with low doses (15 mg) of daily prednisone and increase these by 5 mg every second or third day to 50 mg a day. This dose is maintained for one to three months and then converted gradually to an alternate-day schedule (100 mg every other day) by alternately raising and lowering prednisone dosage by 5 mg in about four-day cycles; this takes 40 days. This alternate-day high-dose prednisone regimen is maintained for 6 to 12 months[138] before gradually tapering at 5 mg a month[139] to 5 to 15 mg over one to two years. Although these recommenda-

tions have been featured in several prominent reviews,[138,139] direct comparison of the effectiveness of the two major recommended methods of prednisone treatment in myasthenia gravis has not been made.

Plasma exchange. The immunoglobulin G fraction of serum from patients with myasthenia gravis produces typical features of myasthenia gravis in immunologically tolerant mice when injected daily for as long as 14 days[140] and accelerates degradation of junctional acetylcholine receptors in intact mouse neuromuscular junctions in vivo.[141] This evidence for circulating humoral factors (not necessarily the measured acetylcholine-receptor antibody) participating in the pathogenesis of myasthenia gravis in humans prompted the successful use of plasma exchange as a therapeutic attempt to remove some of these circulating factors and rapidly, if temporarily, improve the clinical course of severely affected patients in whom more conventional therapies had been ineffective.[142,143] Although the procedure has been used on a chronic basis as primary therapy,[143,144] the major role of plasma exchange at present seems to be as intensive short-term intervention in patients with myasthenia who are on the brink of respiratory insufficiency ("crisis") or who are preparing for thymectomy, irradiation or other anticipated stress.[134]

Azathioprine. Experience in the United States with azathioprine for the treatment of myasthenia gravis was limited until its use was advocated in conjunction with plasma exchange,[144] and an 11-year experience with the successful use of azathioprine in 78 patients with myasthenia was reported.[145] Of these patients 71 (90%) were described as being in remission or as having only mild residual weakness; 51 of them also received prednisone or had thymectomy, or both. Patients who received only azathioprine were older (average age, 56 years). There was no transient weakness as seen with the use of corticosteroid therapy, but azathioprine had to be given in doses of more than 50 to 200 mg per day to prevent relapses during drug therapy. The onset of improvement was gradual and took 3 to 12 months; most of the clinical improvement occurred within the first year of treatment.[145] Remissions were drug-dependent, most patients relapsing 2 to 15 months after the azathioprine therapy was discontinued. Side effects included dose-related bone marrow and liver dysfunction, or idiosyncratic reactions during the initiation of therapy.[146] The use of azathioprine was recommended in cases of myasthenia gravis for inducing and maintaining clinical remission and for its steroid-sparing effect.[146]

The Results of Thymectomy for Myasthenia Gravis

DONALD G. MULDER, MD:* It is difficult to evaluate accurately the results of any intervention, medical or surgical, in patients with myasthenia gravis because of the spontaneous fluctuations in the severity of the symptoms.[12] This is especially the case when observations are made during a relatively brief period of time.

To evaluate the significant effect of thymectomy in this disease, we reviewed our entire experience between 1957 and 1981 during which time 249 patients underwent thymectomy (183 were women) (Figure 3).[147] The age at the time of operation ranged from 2 to 78 years (mean, 35 years), with the mean age of the women being less than that of the men (31 and 42 years, respectively). Preoperatively, 9 patients had mild generalized symptoms including ocular involvement (class I); 136 patients had moderately severe generalized disease including bulbar involvement (class II); 84 patients had acute generalized and bulbar impairment (class III), and 20 patients had the later stages of the disease with chronic, pronounced, generalized and bulbar involvement (class IV). The mean interval between onset of symptoms and thymectomy was 3.5 years.

In each instance thymectomy was done through a median sternotomy. Every effort was made to remove all thymic tissue, including the paired thymic stalks arising in the lower neck. Suspicious tissue in the mediastinum was excised and examined by frozen section to ensure completeness of the thymectomy. Recently, concomitant or postoperative tracheostomy has been rarely necessary, although occasionally weak patients, whose disorder is poorly controlled by medication, will have a tracheostomy placed preoperatively.[148] Anticholinesterase therapy is withheld for at least 24 hours postoperatively and then resumed at reduced dosages as necessary. Steroids are not administered before operation except in special circumstances.

At the time of operation 51 patients (20%) were found to have a thymoma, which in 19 instances was invasive; 133 patients (53%) had thymic hyperplasia; no diagnostic

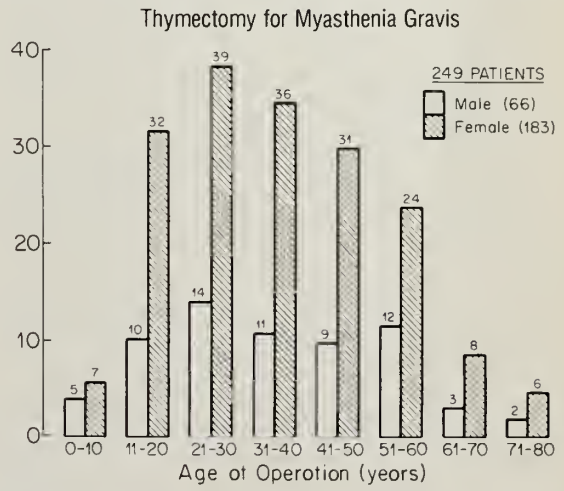

Figure 3.—Age and sex distribution of patients undergoing thymectomy for myasthenia gravis. (From Mulder et al[147]; reprinted with permission from the *American Journal of Surgery.*)

TABLE 6.—*Histologic Features of the Thymus in 249 Patients With Myasthenia Gravis*

Histologic Findings	*Patients*	
	Number	*(Percent)*
Hyperplasia	133	(53)
Thymoma	51	(20)
Benign	32	
Invasive	19	
"Normal"	50	(20)
Involutional	12	(5)
Cysts	3	(1)
Total	249	

*Professor of Surgery, Division of Cardiothoracic Surgery, UCLA School of Medicine.

changes were noted in glands of 50 patients (20%), while 3 patients had thymic cysts and 12 had involutional changes (Table 6). Two patients died in the perioperative period. In one instance this was from Gram-negative septicemia in a patient with diabetes mellitus, whereas the other patient died after exploration for recurrent invasive thymoma. The follow-up period ranged from 2 months to 24 years (mean, 7.5 years); 78 patients had at least a 10-year period of observation whereas 26 were followed between 10 and 24 years, of whom 20 had a follow-up period of more than 15 years. During this 24-year period, there were 13 late deaths, which in most instances (11 patients) were related to pulmonary complications associated with relapse of the myasthenia.

At the time of evaluation the patients were placed in the following categories: *remission*—no medication, no symptoms; *improved*—less medication and better control of symptoms; *no change*—improvement modest or equivocal; *worse*—more medication and symptoms unchanged or more severe; *dead*—early or late mortality. Table 7 summarizes the results for the entire group. The remission rate was 51%, being somewhat greater in women (56%) than in men (36%). In all, 91% of the women and 75% of the men benefited from the operation.

The presence of a thymoma was an unfavorable finding, especially if it was invasive (Table 8); in those with thymoma, however, the remission rate was 37%, and 68% of the patients benefited from operation. In those 198 patients without thymoma (Table 9), the prognosis was more favorable because 107 (54%) had a remission and 91% benefited from operation. The female patients in this group had the highest probability of a favorable response (95%).

The response to thymectomy was also evaluated in relation to the severity of the disease preoperatively (Table 10). In those patients with more mild disease (class I or II), about two thirds underwent remission, whereas only a third of those with more advanced disease (class III or IV) had such a response.

The ventilatory function as determined by vital capacity was measured in 237 patients before and at varying times after thymectomy (Table 11). Those patients with less severe disease and minimal if any respiratory impairment before operation (class I) showed no significant change after thymectomy, whereas a significant improvement did occur in those patients with more severe disease (classes II, III and IV). Additional evidence for the effectiveness of thymectomy in improving ventilatory function was noted in those patients with remission who, by definition, were receiving no medication to which any improvement could be attributed. An increase in vital capacity of 30% over the preoperative measurement in this group was significant ($P<.01$).

On the basis of this long-term follow-up, we conclude that most patients with myasthenia gravis will benefit from thymectomy and that the improvement persists for an extended period of time in a high percentage of patients.

TABLE 7.—*Results of Thymectomy for Myasthenia Gravis*

Postoperative State	Patients: Men Number (Percent)		Women Number (Percent)		Totals Number (Percent)	
Remission	24	(36)	102	(56)	126	(51)
Improvement	26	(39)	64	(35)	90	(36)
No change	7	(11)	10	(5)	17	(7)
Worse	1	..	0	(0)	1	..
Dead	8*	(12)	7*	(4)	15	(6)
Totals	66		183		249	

*Includes 2 operative deaths.

TABLE 8.—*Results of Thymectomy for Myasthenia Gravis in 51 Patients With Tumor*

Postoperative State	Patients: Men Number (Percent)		Women Number (Percent)		Totals Number (Percent)	
Remission	6	(30)	13	(42)	19	(37)
Improvement	6	(30)	10	(32)	16	(31)
No change	3		4		7	
Worse	0		0		0	
Dead	5*		4		9	
Totals	20		31		51	

*Includes 1 operative death.

TABLE 9.—*Results of Thymectomy for Myasthenia Gravis in 198 Patients Without Tumor*

Postoperative State	Patients: Men Number (Percent)		Women Number (Percent)		Totals Number (Percent)	
Remission	18	(39)	89	(59)	107	(54)
Improvement	20	(43)	54	(36)	74	(37)
No change	4		6		10	
Worse	1		0		1	
Dead	3*		3*		6	
Totals	46		152		198	

*Includes 1 operative death.

TABLE 10.—*Remission Related to Preoperative Classification*

Class	Patients: Preoperative States Number	Postoperative Remission Number (Percent)	
I	9	6	(67)
II	136	84	(62)
III	84	31	(37)
IV	20	5	(25)
Totals	249	126	(51)

TABLE 11.—*Vital Capacity Changes*

Class	Patients Number	Preoperative Vital Capacity ml (±SD)	Follow-up Vital Capacity ml (±SD)
I	9	3,077 (±350)	3,366 (±269)
II	153	2,770 (± 78)	3,279 (±220)*
III	64	2,400 (±104)	3,230 (±220)*
IV	11	1,718 (±202)	3,050 (±560)†
Total	237‡		

SD=standard deviation

*$P<.05$
†$P<.01$
‡Twelve patients had no long-term vital capacity measurements recorded.

Conclusion

DR HERRMANN: At present, the outlook for patients with myasthenia gravis has greatly improved because of new techniques and new treatment, advances in respiratory care and support systems and antibiotic therapy to control and combat infections. Death from myasthenia gravis, itself, is infrequent; patients more often die of natural causes or complications.

Our present working concept of autoimmune myasthenia gravis is that of an acquired immune complex disorder at the neuromuscular junction, impairing neuromuscular transmission in voluntary striated muscle. It is associated with a break in immunologic tolerance with blocking and degrading of acetylcholine receptors. There is widening of the synaptic cleft, associated with partial destruction, simplification and shortening of the postjunctional membrane. The cause of this mechanism remains to be discovered. With increasing interest and research in myasthenia gravis by biologic scientists and physician investigators, answers to the cause and cure are hoped for soon.

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Medical Practice Question

EDITOR'S NOTE: *From time to time medical practice questions from organizations with a legitimate interest in the information are referred to the Scientific Board by the Quality Care Review Commission of the California Medical Association. The opinions offered are based on training, experience and literature reviewed by specialists. These opinions are, however, informational only and should not be interpreted as directives, instructions or policy statements.*

Video Electroencephalogram Monitoring

QUESTION:

Is the use of video electroencephalogram (EEG) monitoring accepted medical practice or is it considered investigational?

OPINION:

In the opinion of the Scientific Advisory Panels on Neurology and Psychiatry, video electroencephalogram monitoring is established practice and has been used for many years as a method to evaluate patients with frequent, intractable seizures unresponsive to anticonvulsant medications who are candidates for epilepsy surgery and those with periodic disorders of behavior or consciousness, or both, thought to have seizures who have been treated with anticonvulsant medications without success. This technique has been an extremely helpful tool in the diagnosis and management of seizure disorders in such selected patients. The routine patient with epilepsy or a person with very rare episodes should not be considered for monitoring.

Video electroencephalogram monitoring requires special equipment, specially trained personnel and an experienced professional team. Where such resources are available, it is considered an accepted medical practice.

Managing Patients Who Have Myasthenia Gravis

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Myasthenia gravis is reported to have an incidence of 1:20,000 to 1:40,000 in the United States. Those estimates are probably low, as mild forms may not come to the attention of a physician, acutely severe cases may lead to sudden death and all forms may present difficulty in diagnosis.

In the past 20 years, the physiologic and immunologic bases of myasthenia gravis have been remarkably elucidated. Even though important questions remain unanswered, the treatment and management of patients have improved so that the 35% mortality of 20 years ago has dropped to almost zero. Deaths are more often due to associated or complicating illnesses. Although many patients require care for respiratory failure, their stay in special care units has been greatly reduced. In some series, 75% to 80% of patients have marked improvement or remission with therapy, so that they are able to return to their jobs or ordinary activities.

While Eaton-Lambert syndrome (facilitating neuromuscular block) and botulinum intoxication are examples of presynaptic (prejunctional) disorders due to impairment of transmitter (acetylcholine) formation or release, myasthenia gravis is largely a postsynaptic (postjunctional) disorder. The number of effective acetylcholine (ACh) receptors is reduced, perhaps because anti-ACh-receptor antibodies cause increased turnover of ACh receptors and a decreased number of sites. It is unlikely that the anti-ACh-receptor antibodies are all of one type. The most common precipitation technique using human ACh receptor as antigen shows antibodies in 75% to 94% of patients. Antibodies against ACh receptor have been produced in human thymus cell cultures. There is no firm relationship between antibody levels and severity of illness in groups of patients, although a single patient may have improvement, such as with plasma exchange, as his or her ACh-receptor antibody levels decrease. Some patients with myasthenia gravis have antibodies to thyroid, gastric parietal cells, bone marrow, ovary or striated muscle (especially with thymoma).

From a pharmacologic standpoint, patients with postsynaptic disorders are treated with cholinesterase inhibitors such as neostigmine and pyridostigmine bromide, and those with presynaptic disorders are treated with calcium gluconate, guanidine (now out of favor because of associated hemolytic anemia) or the aminopyridines (4-AP and 3,4-DAP). The use of cholinesterase inhibitors, the mainstay of therapy for myasthenia gravis from 1934 until only five or six years ago, has been deemphasized in recent reports. Because cholinesterase inhibitors represent only symptomatic therapy, they are of little aid in most cases of moderate to severe or of progressive myasthenia gravis, particularly if there is oropharyngeal or respiratory muscle involvement.

In the UCLA conference on myasthenia gravis in this issue, much of the great wealth of knowledge of this disorder is reviewed. Physicians who manage patients with myasthenia gravis must have the neurologic acumen to consider the problems of differential diagnosis, which are largely a function of which skeletal muscles are first involved: a recent onset of weakness of unilateral medial and superior rectus and levator palpebral muscles; progressive proximal pectoral or pelvic girdle weakness (or both); subacute or slowly progressive oropharyngeal muscle weakness with dysphonia, dysphagia or dysarthria, or bilateral medial or lateral rectus weakness. The foregoing refer to the following differential considerations, in the same order: oculomotor nerve disease, as with diabetes mellitus or a posterior communicating artery aneurysm; myopathy, such as polymyositis or, with more rapid evolution, an acute inflammatory demyelinating polyneuritis (Landry-Guillain-Barré syndrome); amyotrophic lateral sclerosis or glioma of the medulla, and internuclear ophthalmoplegia with involvement of the paramedian pontine tegmentum by an infarct or a plaque of multiple sclerosis.

Physicians assuming responsibility for the management of patients with myasthenia gravis must understand the pathogenesis of the illness, including the major and recent advances in physiology, pharmacology and immunology. In many instances we assume the responsibility of the critical care of patients with respiratory failure and the care of patients before and after thymectomy. Furthermore, we are responsible for evaluating the course of the illness and response to therapy both over the short term of hours (cholinesterase inhibitors and plasma exchange) or the longer term of days, months and even years (corticosteroids, antimetabolites, plasma exchange and thymectomy). Regardless of the outcome of therapy that modifies immune mechanisms, we assume responsibility for following such patients for 15 to 20 years, or perhaps to the end of their lives.

Although corticosteroids have been reported to be of value

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in cases of myasthenia gravis for almost 15 years, they have been generally accepted for only 5 years. The data suffer from being uncontrolled retrospective series using various dosage regimens and poorly standardized assessment methods. However, the data available do provide physicians and patients with guidelines and expectations with optimal use of those drugs.

University of Virginia Experience

We have recently reviewed our experience at the University of Virginia with long-term administration of corticosteroids in the management of 116 consecutive patients with disabling or life-threatening myasthenia gravis.[1] Patients received cholinesterase inhibitors early in the course of treatment, if they were of benefit. Neither antimetabolites nor plasma exchange were administered during the period when prednisone effectiveness was being determined. A total of 41 male and 75 female patients aged 8 to 82 years were treated with a regimen of high-dose daily prednisone, 60 to 80 mg per day. Following the *onset* of improvement, the regimen was changed to an equivalent alternate-day dosage (120 to 160 mg), with gradual reduction at a rate of about 10 mg every six to ten weeks, provided the improvement continued toward the goal of marked improvement or remission. Thereafter, reductions of dosage were permitted only if satisfactory improvement was maintained. Overall, the results were favorable in 80.2%, with remission in 27.6% and marked improvement in 52.6%, while 14.7% showed only moderate improvement with significant residual symptoms and 5.2% did not have improvement. Exacerbation early in treatment occurred in 48% of patients, but was severe in only 8.6%, with the onset between day 1 and day 17, and with a mean duration of 4.2 days. The risk of early exacerbation required initiating high-dose prednisone therapy on an inpatient basis. Improvement began after a mean of 13.2 days of therapy, ranging from 12 hours to 60 days. Nine patients (7.8%) did not have the onset of sustained improvement until after 30 days of treatment. In patients with severe disease, or for those who have tolerated prednisone therapy for 30 days with no complications, one should consider maintaining therapy for up to 60 days before concluding that a patient will not respond.

The improvement was gradual, with *maximal* improvement occurring at a mean of 9.4 months. An equally important observation was the period to achieve *marked* improvement, which occurred at a mean of 3.1 months. Of those patients with a satisfactory response, most maintained their improvement with gradual dosage reduction. In all, 14% were able to discontinue prednisone therapy completely, while 18% required a minimal dose (5 to 50 mg on alternate days) to maintain their improvement. Thymectomy was done in many patients following their achieving maximal or marked improvement, but thymectomy was not a factor in determining which patients were able to discontinue prednisone therapy. Of patients achieving a satisfactory response, 18% later had one or more slowly evolving but significant exacerbations, most often related to a too-rapid reduction in dosage. The more common side effects of prednisone therapy, cushingoid appearance (33%) and weight gain (18%), were dose and duration dependent and resolved in large part when the regimen was changed to alternate day and the dosage reduced. Other complications included cataracts (26%), diabetes mellitus (12%), hypertension (12%), osteoporosis (9%), compression fracture (5%), aseptic necrosis of the hip (4%) and a lower incidence of infection, psychological disturbance, gastrointestinal complications and glaucoma. They occurred with ill-advised high-dose treatment for a longer duration or in patients whose first course of treatment was unsatisfactory in either magnitude or duration, and was followed by a second and sometimes a third course of therapy. The likelihood of cataracts was discussed with patients before instituting therapy, and it was generally agreed to be an acceptable complication.

Multivariate analysis showed that patient age was the greatest factor in the response to therapy, with older patients having a greater likelihood of a favorable response. Sex, classification of disease, disease duration and the presence of thymoma were *not* significant factors in the response to prednisone therapy. Our finding that patients with myasthenia gravis and thymoma responded favorably to prednisone therapy is quite contrary to previous published reports. Sghirlanzoni and co-workers in Milan have recently published similar results in 60 patients.[2] Therefore, the physician has data with which to predict the likelihood and time course of response to prednisone therapy and the long-term expectations and possible complications.

Discussion

Considering the preceding data and that from the UCLA conference, how does a physician choose between cholinesterase inhibitors, plasma exchange, corticosteroids, antimetabolites and thymectomy?

One must consider, first, the natural course of the illness. Perhaps 50% of patients with myasthenia gravis present with ocular involvement, but about 80% may have ocular involvement after one month. If there is only ocular involvement after one year, it is likely that the disease will remain mainly ocular. Spontaneous remissions of more than one or two years' duration probably occur in less than 10% of patients, and they tend to be in persons with mild or localized muscle weakness. Simpson has proposed classifying three stages of myasthenia gravis: active stage—increasing severity of weakness with a fluctuating course (most labile, usually lasting five to ten years); inactive stage—less fluctuation (less labile, follows the initial five to ten years), and burned-out stage—relative absence of fluctuation, frequent permanent weakness or atrophy (occurs 14 to 20 years after onset of symptoms).[3] Although one can debate Simpson's proposal, it has merit in characterizing the illness of many patients. (Our own experience has been that patients with myasthenia gravis of more than ten years' duration, including some with atrophy, do respond to prednisone therapy.) Often, a physician may not wish to treat a patient with ocular myasthenia gravis with immunosuppression. In some cases, however, ocular impairment may cause great disability (such as in a dentist or a bus driver) and merit the use of prednisone or azathioprine.

One should compare the therapeutic modalities as follows: the time until onset of improvement following institution of therapy; the time until maximal improvement occurs; the outcome, in terms of likelihood of achieving marked improvement or remission; the duration of maintenance of improvement; the untoward side effects, and the financial costs.

Cholinesterase inhibitors alone may be of value in cases of ocular or mild limb involvement that is essentially not progressive. The onset and duration of action is in terms of hours.

Plasma exchange will lead to marked improvement or remission in about 45% of cases, with the improvement beginning between the first to the fourth exchange and maximal improvement occurring from the first to the 15th exchange (with a regimen of three exchanges a week). However, improvement is for only 4 days to 12 weeks. Some patients who have been pretreated with prednisone or azathioprine have sustained improvement for longer periods. Obviously, plasma exchange may be used on an urgent basis in a myasthenic crisis with respiratory distress, often obviating the prolonged use of an airway or respirator. Plasma exchange may be used as an adjuvant form of therapy, following corticosteroids or antimetabolites or concurrent with them. The recent reports of good intermediate-term results with only plasma exchange followed by thymectomy have not, as of now, been adequately documented.

Corticosteroids will lead to marked improvement or remission in about 80% of cases, with improvement beginning from between 12 hours and 30 days (mean, 13 days) and marked improvement occurring in from 1½ weeks to 18 months (mean, 3 months). Improvement is maintained even with decreasing dosage on an alternate-day regimen. About 14% have maintained improvement after discontinuation of therapy.

The antimetabolite azathioprine is difficult to evaluate because it has often been used along with corticosteroids and thymectomy. One series in the United States indicated that about 45% had some degree of improvement using azathioprine alone.[4] Improvement begins at from 3 to 12 months, and maximal improvement occurs in from 12 to 36 months. Improvement is maintained only when the high initial doses are maintained: about 10% of patients may have maintained improvement after discontinuance of therapy. Mertens and associates and Matell report a "remission" rate of 40%, but these data are flawed by the concurrent use of corticosteroids.[5,6] It must also be emphasized that the German and Swedish experiences with azathioprine have not included favorable results with cases of acute, severe myasthenia gravis. The use of cyclophosphamide in some small series has led to improvement in 74% of patients, with an earlier response. All those studies are retrospective and uncontrolled.

Thymectomy may lead to some degree of improvement in about 76% of cases and to remission in about 35%, with improvement occurring over a few months to more than ten years. One report indicates that of those who achieve remission, 50% will have achieved it in 2½ years, while 25% will *not* achieve it for 5 to 10 or more years.[7] The UCLA conference presents data to indicate that the best results were in patients with "more mild" disease.

The value of thymectomy remains an enigma, since the effectiveness must be evaluated over two to ten or more years. The lure of early improvement, from hours to months after surgical procedure, has yet to be substantiated. Nevertheless, observing the most favorable results and the improvements in surgical technique, anesthesia and respiratory management that have led to almost zero mortality, thymectomy for myasthenia gravis has become increasingly recommended. We urge thymectomy as soon as possible in patients in excellent condition (often having been treated with prednisone beforehand) to minimize operative morbidity. There appear to be no truly reliable criteria for determining which patient will respond to thymectomy in spite of the opinions generated 25 to 45 years ago that young women with illness of short duration had the best prognosis. The criteria to determine whether thymectomy is indicated should be precise, but are not. Most consider the indication to be progressive or severe generalized myasthenia, and a few groups believe that young patients with new disease are the only proper candidates. It seems to me that, if thymectomy *is* appropriate treatment for myasthenia gravis, all patients in whom the diagnosis is firmly established should have their thymuses removed. That conviction arises from our experience that spontaneous remissions that persist are uncommon and from the knowledge that from 10% to 20% of patients with myasthenia gravis will have thymomas. Furthermore, once patients have myasthenia gravis, thymoma may develop at any time in the course of their illness. Thus, one must not have concern for thymoma only at the beginning of the illness.

Obviously there are contraindications to thymectomy, as there are for any major operative procedure on the thorax. Also, because the favorable results from thymectomy appear to accrue over 5 to 10 years or more, one must expect longevity of 10 to 15 years or more.

Thymectomy before adolescence is of more concern, partly because of the threat to growth rate. We have preferred to administer corticosteroids, monitor growth and delay thymectomy until the immediate postpubertal period or later.

There is controversy over whether patients should be treated with corticosteroids before thymectomy, or vice versa. Scientifically, there is no doubt that using both therapeutic methods in the same time frame impairs the evaluation of long-term results of therapy by either modality alone. We have treated patients with corticosteroids first because the predictable response is much more rapid than the response to thymectomy; most of our patients have had moderate to severe myasthenia with oropharyngeal weakness, and otherwise management in the perioperative period would be fraught with complications and result in a prolonged stay in the intensive care unit.

It is apparent that corticosteroids are preferable to antimetabolites when one considers the rapid onset of improvement and the earlier achievement of marked improvement. That is particularly the case in patients with acute severe myasthenia gravis with respiratory failure, dysphagia or both. Only if a physician adheres to a regimen of prednisone that avoids other than transient untoward side effects can one justify the use of corticosteroids—with their earlier favorable results. We found the most effective regimen, with the highest therapeutic index, has been high-dose daily prednisone, proceeding to an alternate-day regimen at the time of a definite onset of improvement, then gradual reduction of dose to maintenance, only with the patient continuing to improve, or having achieved marked improvement or remission. In less acute cases, the use of azathioprine is effective, with the later onset of improvement and later achievement of marked improvement. In these cases, the hematologic and hepatic side effects of azathioprine become a major consideration, partly because of the increased risk of infection.

Although most patients are effectively managed with one

or more of the above therapeutic modes, perhaps 10% respond poorly. Also, each mode has morbidity, though of debatable magnitude. There is clearly a need for the development of more effective therapy with less morbidity. We must proceed to combination therapy involving immunosuppressive drugs, plasma exchange and thymectomy.

The following major questions remain regarding the nature of myasthenia gravis:

- What initiates the production of antibodies to acetylcholine receptor? Is it an inflammatory process in the thymus, or perhaps a viral infection altering cell surface membranes and making the cells antigenic?
- How do anti-ACh-receptor antibodies produce neuromuscular blockade? The antibodies react with sites adjacent to the ACh-binding site (the α-bungarotoxin-binding site). They may lead to turnover or destruction of the adjacent ACh receptor, or they may physically interfere with the reaction of ACh and its receptor. It seems unlikely that the antibodies directly block cationic channels. Lindstrom has dealt with that issue superbly in this UCLA conference.
- Why are some muscles involved and others spared? It appears that the efficiency of neuromuscular transmission (safety margin), which may vary from one muscle group to another in animals, is not the entire explanation, since involvement is often asymmetric and muscles uninvolved in one period of illness may be involved in a later period. Why are there remissions and exacerbations?
- What is the role of the thymus and, if thymectomy is helpful, why is improvement delayed for many months to ten years? Does the thymus produce the antibody, the antigen or both? Is delay of response due to long-term circulating lymphocytes?
- Which patients are most likely to respond to a particular treatment modality?
- Is plasma exchange effective because it removes anti-ACh antibodies, or something else?
- Are there geographic or environmental factors operating in the incidence of myasthenia gravis?

At our present state of knowledge, every patient with myasthenia gravis should be reviewed by a physician with expertise in differential diagnosis and in the use of pharmacologic and immunosuppressive therapy. Review should continue at regular intervals during the use of major therapeutic agents.

We must evaluate the effectiveness of other immunosuppressive agents such as cyclophosphamide and methotrexate in prospective controlled studies. The use of cyclosporin—which may act to suppress selectively aberrant antibody production—the development of anti-idiotype antibodies and the use of pooled γ-globulin may provide insight into immune regulation in patients with myasthenia gravis.

It is likely that the experts will have varying opinions regarding the specific indications for treatment and the choice of therapy. Nevertheless, all of us, whether in private or institutional practice, have an obligation to participate in controlled prospective therapeutic trials. It seems quite unlikely that the management of patients who have myasthenia gravis will improve further without dedicated participation by each of us.

Tremendous progress has been made in the understanding and management of myasthenia gravis. Scientific advances have had a great impact, but so have serendipity and empiricism. With further research, with better keeping of records and with controlled studies of some modes of therapy, the above questions will be answered.

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Medical Staff Conference

Stress and Medical Training

These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs Homer A. Boushey, Associate Professor of Medicine, and David G. Warnock, Associate Professor of Medicine, under the direction of Dr Lloyd H. Smith, Jr, Professor of Medicine and Chair of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, School of Medicine, San Francisco, CA 94143

DR SMITH:* *House-staff training is now and always has been a period of stress. Medical schools do not graduate physicians; they graduate young men and women who are well prepared to learn to be physicians during years of increasing responsibility in our teaching hospitals. In this sense the years of residency are the real medical school experience. What we now designate as medical school is really "premed."*

Residency has its elements of Marine "boot camp" psychology, part of which is exhilarating (in small doses) and part of which is enervating. In this conference some aspects of the ecology of house-staff training will be examined. Those who are in the process will readily recognize the ambience being described. Those who have completed training will look backwards with a degree of nostalgia that bears a linear relationship to the time since they themselves served their years in this form of educational bondage.

DR ZIEGLER:† In this conference we address the many facets of stress in medical training. We define stress as a "perceived threat," the term incorporating both the stimulus (stressor) and the response (coping). Over half of human illness is related in some way to life-style and behavior.[1] Thus, all physicians are called upon in practice to counsel their patients to lead a life that avoids unhealthy practices or behavior. Physicians must learn about stress and coping and acquire skills in counseling behavior modification. In this process, physicians must also develop awareness of their own mechanisms of recognizing and coping with stressful issues.

Few training programs are more demanding than medicine. Medical students are "selected" for character traits of competition, obsessive-compulsive behavior and altruism—behaviors requisite to survive the rigors of medical school.[2] Upon graduation, however, physicians-in-training encounter the "real world" of incurable illness, irascible patients, death and dying, dispassionate bureaucracy, entrepreneurial realities and continued academic competition. These pressures compromise personal values of altruism, humanism and even integrity.[3,4] Thus the stresses inherent in medical training provide an environment in which physicians can examine their own life-style, values and coping skills.

We will address the following: the experience of stress in medical training as viewed by a chief medical resident, the profile of an impaired physician and the tragic consequences of maladaptive patterns of coping with the stresses of medical practice, some of the particular issues causing stress that were identified in a seminar for medical interns, myths and realities of medical practice in relation to the self-interest and well-being of its practitioners and guidelines for coping with stress for trainees in medical practice.

Experiencing Medical Residency

DR STRULL:* The issue of stress associated with residency training has received increasing attention in recent years for two very cogent reasons. First, fully 50% to 75% of the patients seen in practically all branches of clinical medicine have problems related either primarily or secondarily to life stress.[1] A substantial proportion of these patients has no detectable illness to account for their symptoms. In addition, there are many patients with diseases such as myocardial infarction and duodenal ulcer in which stress is a critical causative factor, an impediment to the healing process and a contributor to recurrence. The second and even more urgent concern is the profound and potentially dangerous, even life-threatening, effect of stress on residents in training. This is not to say that all stress is harmful. A distinction is often made between "eustress" and "distress." Eustress occurs in the setting of adaptive coping skills and support systems and becomes a stimulus to learning and growing. Distress occurs in the absence of adequate coping skills and can result in serious emotional impairment of a physician and improper patient care.

There is no clear dividing line on the continuum between eustress and distress, as persons vary in the pressures they can tolerate. The ability to cope with stress is further modified by the social support network inside and outside the hospital.

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Because of this variability, physicians must explore regularly how they experience and cope with the stresses in their life and develop a sensitivity to the detrimental effects of stress on health and well-being.

I readily recall my own recent experience as a medical resident. Internship was extremely demanding and stressful, albeit rewarding. During the first few months I felt I was "coping well" as I learned to stay up 36 to 40 hours in a row and to devote myself to taking care of patients. I remember vividly those long nights on call in the Coronary Care Unit, where I started my internship, when every monitor alarm or even ambulance siren from the street below would send a chill up my spine and my own pulse racing as fast as that of patients in ventricular tachycardia.

My most demanding patient was a young woman admitted to hospital for an exacerbation of her systemic lupus erythematosus affecting her brain, heart, lungs and bones. Moreover, her marriage was dissolving because of her illness. The complexity of her medical situation and the love-hate feelings she expressed toward a physician the same age as her husband proved extremely stressful to me. She would inevitably have a fever or seizure or heart failure would develop just as I was ready to leave the hospital on my nights off. Consequently, I became so involved with her medical and psychological needs during her two-month stay in hospital, in addition to those of my other patients, that I rarely left the hospital before midnight.

I suppose I was indeed "coping well"—but only later did I realize at what cost. I believe my patients received excellent care. Yet my own life and relationships became neglected to the point where little was left of my personal life outside the hospital by the end of the year. Since that time I have had to take stock of the situation and make very conscious choices about how to integrate my personal needs into my life as a physician. I now believe that greater sensitivity to myself and my needs has helped me become a better physician.

This personal anecdote is not uncommon. In fact, I consider myself one of the fortunate ones, for the stress of internship sensitized me to the larger issue of stress in life and to the development of ways to cope with it. Not everyone has been so fortunate, and I have seen the stress of residency take its toll in many ways. Several suicides and the dissolution of many marriages among house staff in recent years have been only the tip of the iceberg. The high prevalence of depression and dependence on drugs and alcohol in the medical profession attests to the widespread nature of the problem.

On the other hand, I feel that no one should have to tolerate the often overwhelming degree of stress inherent in the academic setting. Such stress interferes with the training experience itself and compromises the development of both medical and humanistic maturation during residency. Certain interventions that could reduce stress without diminishing the quality of care need to be considered seriously. These might include "every fourth night on-call" rotations, a "night float" system, one-to-one supervision of interns by residents, an expanded role for nurses and weekly meetings to discuss stress and well-being encountered during residency. Finally, I would advocate seminars for attending physicians that address the problem of stress and methods to foster humanistic development in medical trainees.

Impaired Physicians

DR LARSEN:* I shall discuss the demography and management strategies of impaired physicians. Over the past decade, the medical profession has finally acknowledged the concept of the impaired physician.[5] Medical society committees on impairment now exist in all states. The 1975 report to the American Medical Association estimated a 5% to 6% nationwide prevalence of physician impairment due to substance abuse, mental illness or both. In the California Diversion Program, alcoholism, drug abuse and other psychiatric disorders head the list of presenting problems.[6]

While impairment may develop at any stage in the professional life cycle, severe dysfunction is most prevalent in the mid-life years. In a review of 362 impaired physicians in six treatment programs, the mean age was 46.6 years (range, 41 to 54).[6] A middle-aged professional has considerable difficulty taking on the patient role. Impediments to successful treatment are a feared loss of status, decreased self-esteem and an appearance of being in need. For a person who has functioned previously with authority and decisiveness, assuming this role in mid-life presents internal conflicts. Additional resistance to treatment comes from the perception that the patient or sick role is a confirmation of waning physical and mental abilities.

The defenses of postponement and denial contribute substantially to the high prevalence of impairment in mid-life. Unmet professional and personal expectations following years of delayed gratification may lead to maladaptive functioning.[7] A gradual, stepwise process begins with dissatisfaction and frustration, progressing to disillusionment, maladaptive coping and eventually to impairment. The time frame for this process is congruent with a mid-life manifestation of impairment. The syndrome is undoubtedly aggravated by other mid-life changes.

One may rightly ask whether physician impairment is on the increase, or whether the profession is more sensitive to the syndrome. Both statements appear to be true. Physician disillusionment may result from a gradual erosion of authority and autonomy of the medical profession. Sophisticated medical technology, patient expectations, physician maldistribution and fiscal pressures from government and health insurance companies are changing the health care delivery system. In this environment a physician who is wedded to the notion of a traditional autonomous model of practice may be in danger. Practicing physicians have become increasingly dissatisfied with their careers, themselves and their patients. Maladaptive coping manifested by substance abuse, social withdrawal and suicidal behavior is an extreme reaction to this discontent.

The problem of physician impairment is not rare and may well be more prevalent than treatment programs estimate. Treatment programs alone will not, of course, eliminate impairment in the medical profession. Some persons will be helped, but early intervention and preventive measures must complement treatment of a disabled physician. As physicians, we have an obligation to identify and treat our impaired colleagues. It is equally essential to foster development of self-awareness and adaptive coping skills in the training of physicians.

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Stress in Medical Internship

DR ZIEGLER: In November 1981, Dr Nick Kanas (Assistant Professor, Department of Psychiatry, UCSF) and I started a weekly discussion group for UCSF medical interns during their eight-week rotation at the VAMC.[8] Attendance was voluntary, the meeting lasted one hour and beepers were turned over to residents. Participants were asked to discuss experiences that caused stress in their lives as interns, and group leaders (an internist and a psychiatrist) helped facilitate the discussion and focus on the issues. It was emphasized that this was not a psychotherapy group. The average attendance was five interns (out of eight on service) and we kept track of the major topics under discussion for the first 36 sessions. We also sent out questionnaires that addressed the experiences causing stress and attempted to evaluate the usefulness of the discussion group.

Generally, the interns' experiences centered on three major issues that caused stress: the consequences of high self-expectations, the loss of control over one's life and difficulties in regard to dependency.

The consequences of high self-expectations produced the most stress. The need to strive for perfection was particularly frustrating early in the internship because of inexperience and lack of knowledge. There was not enough time to accomplish all that needed to get done. Caring for very ill or dying patients was also very stressful. There was self-imposed pressure for high standards of professional competency in a setting of time constraints, difficult clinical problems and many demands. Inability to meet these expectations produced feelings of guilt, anxiety and frustration.

The second major issue for the interns was lack of control. There was a sense of being at the mercy of the "system," that the bureaucracy controlled their actions. The "scut list" and beeper also symbolized a loss of autonomy. The encroachment of work demands on social life was also a major problem. Discussions on this issue reflected both anger and resignation.

The third issue that provoked stress was an ambivalence over dependency. In dealing with demanding patients and their relatives, there was a sense of conflict over the interns' own anger at patients and their need to provide nurturance. The interns' awareness of the stress they were under and their own need for nurturance and support also conflicted with their desire for independence and autonomy.

The coping patterns adopted by the interns varied. Most found support from personal relations outside the hospital and co-workers on the house staff. Two thirds also felt that appreciative patients and diagnostic and treatment successes offset the effects of stress. In all, 55% of the discussion group participants felt that the group helped them deal with stress, generally through sharing experiences and venting emotions.

We infer from these observations that high self-expectations are the result of the popular image of physicians as heroes and an expectation by society of a "larger than life" performance. High self-expectations come into inevitable conflict with the real world. Experiencing a gap between an idealized performance and what is realistically attainable produces guilt and frustration. Physicians often impose this heroic fantasy on their families, leading to marital discord and strained relationships.

The second issue causing stress—lack of control—may derive from the needs and behavior patterns of the so-called type A personality. This time-compulsive, achievement-oriented and approval-seeking behavior is almost essential to get through the rigors of premedical and medical training. In medical school, this behavior is rewarded with good grades and evaluations. In the more unstructured world of clinical medicine, type A persons become frustrated by an uncaring, inefficient hospital bureaucracy and by ungrateful, demanding patients.

The final issue is the phenomenon of dependency. Many of the professional rewards in medicine are the satisfaction of needs to nurture, to receive approval and to excel. These needs may come in conflict with more hedonistic needs such as relaxation, a reasonable social life, recreation or extracurricular pursuits. Dr Albert Jonsen portrays this conflict as a contest of altruism versus self-interest.[9] The dependency needs of physicians are usually kept secret from themselves. We like taking care of other people but would seldom admit that we need their dependence on us. Dr Peter Jensen, a psychiatrist, aptly describes the inherent dangers of this posture:

> As physicians, we must be aware of the pitfalls of what might be termed the *"omnipotence/dependency" doctor-patient relationship*, wherein the patient unconsciously assumes that the doctor not only can cure his or her illness but also can magically gratify other unfilled needs, such as love, acceptance, happiness, or security. The unwitting doctor who needs this respect and admiration may encourage these unconscious fantasies. Such fantasies are difficult to maintain, however, and usually one party becomes disenchanted, resulting in a spiraling drama of hurt, anger, and disappointment.[10]

Myths and Realities in Medical Practice

DR MARTIN:* Physicians unquestionably deal with many stressors such as long hours, fatigue, uncertainty, pain, fear and death. As physicians we generally do not consider the possibility that we carry around a set of myths about ourselves that makes the stresses more difficult. We construct medical training as a breeding ground to perpetuate the same myths in future generations of physicians. The following are five common myths held by physicians.

Physicians Should Be All-Knowing

In our highly competitive environment, the skills that are rewarded and that lead to excellent grades, choice house officer positions and popularity as attending physicians are the ability to produce facts in abundance and to outquote, outreference and outthink our colleagues. Few physicians actually believe that they know enough or read enough, even though they accumulate prodigious amounts of information. Given the scope of a field like medicine and the sieve-like fallibility of human memory, facts should not be a determinant of a physician's sense of self-worth, and mastery should be approached with more realistic goals.

The skills most likely to be valuable to a practicing physician are a framework to think about problems, a good filing system, the knowledge of whom to call upon for help and the sense to know when the problem goes beyond the bounds of our knowledge. As Oliver Wendell Holmes said, "The best part of our knowledge is that which teaches us where knowledge leaves off and ignorance begins." Medical training should create an environment in which the willingness to learn and discover is considered as valuable as the ability to recall.

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Uncertainty Is a Sign of Weakness

It has been said that medicine asks one to become old before one's time, to have the wisdom of grandparents and to act rationally in the face of irrational feelings and behavior. Though we carefully prepare ourselves for this goal, there are many situations for which there is no preparation. We deal frequently with patients in difficult and extreme circumstances who have problems that are insolvable. And yet the ideal, mythical physician always operates with certainty and has a ready answer to any situation. Denial of uncertainty is a natural response to being confronted with problems beyond our knowledge and experience. Unfortunately, it leads to decisions that are oversimplified and to frustration with a patient for not fitting a familiar solution. Not acknowledging our limits breeds a kind of self-protective arrogance or overconfidence that actually walls off help from the outside. For physicians in training, it is important to learn that availability of assistance requires the acknowledgment of uncertainty, and this will best come by example from faculty and older physicians. Given our current myths, it is not something we provide very easily.

Patients Should Always Come First

Physicians' behavior with regard to their own health is often a parody of the age-old patients' comment, "I didn't know that doctors got sick." We are a profession of helpers and are subject to tremendous demands to give to others, unfortunately denying our own needs to receive. Internship and residency training initiate the process of denying our own needs in order to be always available to patients. Following on this initial training in unhealthy behavior, the pattern of neglecting physical, emotional and social needs is often carried into one's career. Many physicians have health habits they would never prescribe for their patients. Most do not have a regular personal physician, do not take time off when they are sick and sometimes prescribe for themselves. Physicians' family and social relationships suffer notoriously at all stages of their careers. Medicine is inherently interesting and distracting, and we may not realize that we or our families are in trouble until serious problems occur. The fact that all of us have physical and emotional limits may be recognized too late when ill health and impairment have already developed. In many instances patients must come first, but not always.

Technical Excellence Will Provide Satisfaction

When one thinks about it, clear-cut technical success is uncommon in medicine. Though all of us like those instances in which we can make incisive diagnoses and prescribe curative therapy, we deal more often with problems or illnesses that are unlikely to be cured. If one uses cure as the only criterion for success, medicine becomes a series of failures. Ultimately, all of our patients age and die and, at best, we wage only a holding action. In our attention to technical expertise, it is possible to forget that much of the gratification in medicine comes from just being a caring human being. I don't know how to measure its effect, but the sense that there are caring people around not only makes illness endurable, but perhaps is a factor in recovery. If nothing else, it provides a purpose to our role as physicians that is much deeper and permanent than whatever temporary success we might have.

As George Bernard Shaw suggested in *The Doctor's Dilemma*, we should "make it compulsory for a doctor using a brass plate to have inscribed on it, in addition to letters indicating his qualifications, the words 'Remember that I too am mortal.'"

Patients, Not Physicians, Need Support

This myth may underlie all the rest. As a group, physicians have great difficulty asking for help or sharing discomfort, even among themselves. It is uncommon for physicians to admit that certain patients or situations give them difficulty or that they are simply having trouble coping. As physicians, we may voice complaints about external problems but rarely acknowledge the unique and personal way in which we are hurt.

Emotional withdrawal is unfortunately a natural defense in a demanding and isolating profession. This defense makes it all the more imperative to seek support from family, friends and, most important, each other. Because all physicians have times when they feel pressed, frightened and overwhelmed, to deny this is to wall off a large portion of one's life.

Coping With Stress

DR COATES:* Stress is a single word that describes a complex phenomenon. Stress management or "coping," the catchword of the day, is even more complex. The management of stress implies self-awareness so that a person can recognize the signs and symptoms of stress and act before it gets out of control, commitment to managing stress as a priority for enhancing mental well-being and preserving physical health and learning a variety of strategies for preventing and reducing stress.[11]

Becoming Aware

Stress affects persons cognitively, physically and behaviorally. Cognitive effects include stereotyped or disorganized thought. Physical effects can include sympathetic arousal and associated rises in heart rate, blood pressure, gastrointestinal distress and muscle tension. Behavioral effects include anger, avoidance or frantic, hyperactive behavior.

A person needs to recognize the build-up of stress early in the stress-response cycle. This process is learned through formal training and practice in hypnosis, yoga, relaxation, meditation autogenics or biofeedback. These sensitizing techniques teach a person what it feels like to be relaxed and "centered" so that contrasting states of tension and anxiety can be discriminated more readily. Self-monitoring, the systematic observation and recording of thoughts, behaviors, physical states and emotions, is also a useful technique to identify stressors. Detailed records of daily activities can enhance awareness of stress and tension and the circumstances most likely to elicit these responses.

Commitment to Stress Management

Stress is the evil of the age and no one can find fault with the need to engage in stress management. However, serious effort at managing stress requires establishing as a priority the need to keep it within reasonable bounds. It means giving stress reduction a higher priority over other competing activities such as prestige, money, peer adulation, more or larger

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research grants and participating in more committees. Personal decisions requiring allocation of time and energy must place a premium on stress and adaptive coping.

The type A behavior pattern referred to earlier is typified by time urgency, hostility and polyphasic activity such as doing or thinking about two to three things at the same time. A type A person places a premium on external accomplishments and gets frustrated and angry when faced with obstacles. While this is not an easy pattern to break, the commitment to stress management demands a commitment to *quality* instead of quantity. This does not preclude achievement, but rather encourages the achievement of quality.

Preventing and Reducing Stress

Flexibility is the hallmark of effectively managing stress. Stress can be prevented or minimized by clarifying personal values and goals, determining means to reach these goals and evaluating behavior in terms of these objectives. Stress can be managed, when it arises, by effective actions to solve problems as they occur. Three major sources of stress are failure to acknowledge stress when it arises, failure to evaluate the sources of stress and procrastination or lack of effective action. Although I shall deal in brief generalities, Table 1 shows some suggested ways in which house staff can reduce job-related stress.

Time management is key. Define the most important tasks to be accomplished, allocating a reasonable time to get them done. New opportunities or demands can be accepted or rejected as they fit in with one's priorities, objectives and current activities. Become aware of disproportionate amounts of time spent on trivial as opposed to priority tasks. Be selective and judicious in allocating time. Save out a few minutes regularly just to relax.

Despite the best of plans, no one can avoid stress completely. Available methods for reducing stress vary considerably. Again, the various forms of relaxation may provide one

TABLE 1.—*Suggested Ways for House Staff to Reduce Job-Related Stress*

Goal	*Suggested Methods*
Recognize Stressors	Make a commitment to identify and reduce stress in your life.
	Be sensitive to emotional responses to stressors—feelings of guilt, frustration and anger, depression and hopelessness, tension and anxiety.
	Try to identify major stressors using systemic self-monitoring.
	Take *early* action to reduce stressor and initiate coping before emotional response takes over.
Time Management	Negotiate tasks with colleagues.
	Delegate responsibilities to others.
	Reduce beeper interruptions, such as, be available on ward for questions at set times; instruct callers to leave messages and indicate "stat" or "at your convenience" for return calls.
	Set aside an hour as inviolate and relax, walk, run, meditate or otherwise get it together.
	Be selective in choosing what you read and learn. You remember best what interests you and what applies to your patients.
Behavior Modification	Learn to be appropriately assertive (as opposed to aggressive).
	Learn techniques of active listening, imagery and constructive criticism.
Social Support	Establish as a priority spending quality time with friends and family. Structure the time so that you are not called away and are rested and relaxed. Seek out relationships with colleagues. Join support groups, community organizations or team sports.
Environment	Take steps to establish as relaxing and esthetic an environment as possible, such as a radio or tape recorder in your office, pleasant art work or a carpeted floor.
	Inform colleagues or co-workers of your favored work habits so that you will not be interrupted needlessly.
Relaxation Techniques	Explore various techniques such as yoga, meditation or biofeedback.
	Ensure adequate diet and exercise regularly.
	Engage in self-awareness techniques to discover "highly prized beliefs" (myths) that may not work for you.
	Cultivate relaxation habits with the same energy and commitment that you apply to your work.

approach to the problem. Physical and recreational activities provide an important form of relaxation.

Social support and attention to interpersonal relations are important in reducing and preventing stress. Social support buffers the impact of stress by allowing us to share uncertainty and discomfort and to rely on colleagues to help us to solve problems.

Preventing and managing stress demands that we take stock of the physical and social environments to which we are subjected. Stress is increased by environments that are noisy, crowded, hostile, too hot or too cold. Environments need to be examined carefully for their qualities and consequences.

Examining and modifying behavior that predisposes to stress can be an achievable goal. For example, learning to act assertively (as opposed to aggressively) usually gets favorable results. Other techniques such as active listening, imagery and constructive criticism provide a useful repertoire for preventing stress.

Finally, more and more decisions about medicine and medical practice are driven by economics. The number of physicians available and the number of patients who need to be seen within given amounts of time are dictated by financial as much as medical reasons. While this may be a necessary and inevitable part of contemporary medicine, there are no simple solutions to the problem. However, if we take seriously the importance of stress management, then the issues related to stress deserve to be weighted equally with financial and medical issues.

Concluding Remarks

DR ZIEGLER: I shall conclude with some reflections on tradition in medical training. Seasoned physicians readily recall the arduous years of house-staff training when interns literally lived in the hospital, received only their uniforms and meals in payment and devoted virtually all of their waking hours to patient care.

The Fourth Medical Division regarded itself as the top service at the Boston City Hospital, the elite in the sharpest and brightest of all the teaching hospitals in town. We were the iron men, we told ourselves. The lights in the laboratory on the top floor of the Peabody Building were never turned off at night; the house staff never slept.[12]

These same physicians may now look at the generous on-call schedules and ample salaries of today's house staff and wonder whether training programs are sufficiently rigorous. The time-honored tradition of medical internship is regarded as a rite of passage to physicianhood. Today's house staff, however, complain bitterly about the time pressures, menial tasks and multiple demands in their experience as interns. They wonder seriously why the system cannot be changed. They may become cynical, embittered, disillusioned and angry.[13]

Psychiatrists and educators have wondered openly about the means and the goals of medical internship because this form of arduous training has not been subjected to critical analysis of the attainment of its goals. The issues we have examined in this conference bear directly on the wisdom of traditional medical training. Times have changed, as our participants have pointed out. Despite severe economic pressures, it is time to change house-staff training to provide more leisure time, to value process skills over memorization, to foster self-awareness over denial and to reward humane behavior over technical competence.

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Epitomes

Important Advances in Clinical Medicine

Urology

The Scientific Board of the California Medical Association presents the following inventory of items of progress in urology. Each item, in the judgment of a panel of knowledgeable physicians, has recently become reasonably firmly established, both as to scientific fact and important clinical significance. The items are presented in simple epitome and an authoritative reference, both to the item itself and to the subject as a whole, is generally given for those who may be unfamiliar with a particular item. The purpose is to assist busy practitioners, students, research workers or scholars to stay abreast of these items of progress in urology that have recently achieved a substantial degree of authoritative acceptance, whether in their own field of special interest or another.

The items of progress listed below were selected by the Advisory Panel to the Section on Urology of the California Medical Association and the summaries were prepared under its direction.

Reprint requests to Division of Scientific and Educational Activities, California Medical Association, 44 Gough Street, San Francisco, CA 94103

New Forms of Treatment in Cases of Urinary Stone Disease

WITHIN TEN YEARS, medical and surgical treatment of urinary stones has changed radically. Three of the five types of urinary stones, which account for 30% of all stones, may be prevented and, in some cases, dissolved by oral medications. Uric acid and cystine stones will often dissolve with oral administration of alkali and large volumes (more than three liters) of fluids per day. Allopurinol or penicillamine, respectively, will further inhibit formation of these stones. Struvite (magnesium ammonium phosphate) precipitation can be inhibited by giving acetohydroxamic acid or its analogs, and these stones may sometimes be dissolved by irrigating with acid solutions.

Unfortunately, some of the foregoing and the remaining 70% of patients with two types of calcium stones have little hope of dissolving their stones. But we do have many ways of preventing the formation of new calcium stones in such patients: dietary limitation of calcium and oxalate, high water intake and the use of medications such as neutral phosphates, hydrochlorothiazide, citrate and others. A short metabolic evaluation will indicate the best approach for most patients.

For some patients, preventive measures come too late: when they arrive at an emergency room they have nausea, vomiting and renal colic due to stone obstruction. Some will require surgical assistance to be relieved of the stone. In the past, such relief required cutting procedures in more than 70% of patients. Now, only 20% of patients will require "big" operations. In the remainder, stones lodged in the kidney may be pulverized and removed either by percutaneous ultrasonic technique, which requires a puncture in the flank area, or by extracorporeal shock wave lithotripsy, which requires no incision. Ureteral stones, even those near the kidney, may now be pulverized via a miniature telescope with ultrasonic wand, then removed as fragments.

This combination of medical and surgical therapy for urinary stone disease has reduced the stone recurrence rate from 80% to 20%, has reduced the average hospital stay from eight days to four days and the time lost from work to ten days rather than six weeks.

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Renal Transplantation

SIGNIFICANT ADVANCES have been made in renal transplantation in the past five years. Graft functional survival has risen to between 80% and 90% at one year while patient mortality has fallen to 5% at one year. The best results continue to be achieved with living and related donors. Tissue typing allows the selection of a human-leukocyte-antigen-identical sibling donor with a 90% to 95% graft functional result at one year and a 70% graft function at ten years. The use of donor-specific transfusions for recipients of one-haplotype-matched living donor kidneys produces similar highly successful grafts.

Recipients of cadaveric kidneys enjoy an improved graft function with the use of deliberate pretransplant blood transfusions and donor-recipient matching of donor-recipient pairs. These factors will result in 70% graft function at one year. The use of the new immunosuppressant, cyclosporine, can improve this percentage of successful grafts to 80% at one year. The oncogenetic potential of cyclosporine observed in early clinical experience appears to be largely eliminated with smaller dosage schedules.

Pulmonary and other infections were the primary cause

for patient mortality in the early decades of clinical renal transplantation. These risks have been reduced such that cardiovascular disease has become the major cause of mortality after renal transplantation.

An increasing number of patients with renal failure due to type I (insulin-dependent) diabetes mellitus are being treated by transplantation with results similar to those reported above.

DONALD C. MARTIN, MD
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Section Editor's Comment:

There is still a need for donor kidneys, and local institutions should inquire how they may become a part of this process.

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Endourology

THE SUBSPECIALTY FIELD of endourology has grown tremendously in the past several years. An endourologic procedure is a closed, controlled manipulation within the upper urinary tract; this has become a well-established method of removing upper urinary tract calculi. The advantages of the procedure over conventional open surgical procedures for removing stones are no incision, lower morbidity and a shorter time away from work. Endourology also encompasses other urinary tract procedures such as ureteroscopic stone manipulation, intrarenal operations to relieve obstruction or to do a biopsy of a lesion and stent placement to treat ureteral strictures and fistulae.

Percutaneous removal of renal and ureteral calculi is the most commonly done endourologic procedure. By combining the expertise of a radiologist and a urologist, a nephrostomy tube tract can be established in the collecting system, affording access to specific calyces, renal pelvis or proximal ureter. Once access is obtained, a variety of endoscopic instruments can be used to remove the stone. Smaller stones can be removed intact, whereas larger stones (greater than 1.2 cm) must be disintegrated using either ultrasonic or electrohydraulic energy. Following removal of the stone, the nephrostomy tube is left in for a short period of time (usually one week or less) and on its removal the patient may resume normal physical activity.

To date, we have done more than 300 procedures on a wide variety of surgical calculi, with an overall success rate of greater than 95%. The complication rate has been 4%, with the major complication being hemorrhage to an extent to require a transfusion. In only two cases was an emergency operation necessary to correct complications, and in these cases the end result was good. More than 50% of the procedures are done entirely under local anesthesia and the rest (larger and more complex stones) under general anesthesia. The overall average postoperative hospital stay is three days.

During our initial experience with percutaneous extraction of renal and ureteral calculi, we rejected about 20% of the possible candidates due to various anatomic and technical reasons, in addition to lack of experience. At present, however, virtually all stones that require surgical removal, from simple renal pelvic stones to complex full staghorn calculi, can be removed percutaneously.

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Section Editor's Comment:

The author has considerably more experience than many urologists in this procedure. These statistical successes may not always be in that range in the hands of others.

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Magnetic Resonance Imaging and Other Radiologic Advances in Urology

MAGNETIC RESONANCE (MR) IMAGING, also called nuclear magnetic resonance, has been in clinical use for about three years. Patients having MR imaging are exposed to a strong magnetic field and radiowaves but no ionizing irradiation. No currently known detrimental biologic effects occur with the magnetic field; however, ferromagnetic objects such as oxygen tanks, poles for holding intravenous fluids or ventilators cannot be placed in the immediate vicinity of the magnet in most MR imaging units. Patients requiring these devices or who are unable to remain quiet for the 45 to 50 minutes required for an average scan cannot by studied. Patients with surgical clips are not a problem but those with aneurysm clips should not be studied due to the possibility of moving the clips.

MR imaging is becoming accepted as the most sensitive imaging modality for many brain and central nervous system lesions. The experience in the pelvis and retroperitoneum is more limited. MR imaging shows better soft tissue contrast resolution than computed tomographic scanning, allowing visualization of the corticomedullary junction in normal kidneys and healthy renal transplants without contrast material. Simple renal cysts can be distinguished from hemorrhagic cysts. Renal masses are easily visualized with about the same resolution as computed tomography. Coronal, sagittal and axial views can be obtained, which are helpful for tumor staging, particularly in the pelvis. Depending on the pulse sequence, MR imaging appears to be more sensitive for detecting abnormalities; however, it has not been specific in differentiating malignant from benign lesions either in the kidney or in the prostate. The procedure has the disadvantage that only large calculi are visualized. MR imaging holds the promise of noninvasively characterizing abnormalities, particularly if any of the MR imaging contrast agents currently being developed prove useful. MR imaging is able to detect blood flow and may be potentially useful for its quantitation. It may be possible with further developments in technology to do in vitro spectroscopy of certain elements, particularly phosphorus.

Several new nonionic contrast agents for urography and angiography are in clinical trials in the United States. One of these, metrizamide (Amipaque, Winthrop Laboratories), is

currently available for use in myelography. Studies show that these agents have less hemodynamic, cardiovascular, neurologic, hematologic and renal toxicity and produce fewer unpleasant side effects than currently used ionic agents. They also produce higher urinary iodine concentrations and less diuresis. Whether these agents will reduce the number of serious and fatal contrast reactions in patients having urography is uncertain. When these agents become commercially available, they will probably cost four to ten times more than the currently available agents.

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Treatment of Cancer of the Prostate

TOTAL PROSTATECTOMY continues to offer the best disease-free and overall survival in patients with localized prostatic cancer. Patients who undergo total prostatectomy have a significant risk of erectile impotence when a standard radical prostatectomy is done. Those patients who value the capacity for continued sexual activity have been satisfied with a penile prosthesis because the sensation of orgasm is usually intact. In a recent study, Walsh and co-workers suggested modifications during radical retropubic prostatectomy to preserve the pelvic plexus nerves responsible for erections. There is legitimate concern, however, that the less extensive surgical margins and additional dissection required to preserve these nerves might compromise the extent of the operation necessary to remove the cancer.

New concepts and drugs are emerging for treating cases of metastatic prostate cancer. Currently, orchiectomy and diethylstilbestrol are the most commonly used forms of hormonal therapy for managing patients with prostatic cancer. Some patients find the thought of orchiectomy disagreeable, and the use of estrogens is associated with fluid retention and an increased incidence of cardiovascular disease that appears to be dosage related. Luteinizing-hormone-releasing hormones (LH-RH), which appear to obviate these problems, have been synthesized. These drugs actually stimulate testosterone production when initially given; however, ongoing administration has the paradoxic effect of inhibiting pituitary release of luteinizing hormone (and follicle-stimulating hormone), resulting in a fall in serum testosterone to castration levels within two to four weeks. About 50% to 75% of patients have vasomotor hot flashes and most note significantly diminished libido and erectile impotence. Because of the absence of potentially life-threatening side effects sometimes associated with oral estrogen therapy, these compounds might be attractive substitutes.

Antiandrogens have also been evaluated in cases of metastatic prostatic cancer. They may offer an advantage over conventional hormonal therapy in that potency appears to be preserved in most patients. In an effort to prevent disease flare associated with the initial administration of LH-RH, Labrie and colleagues use an antiandrogen at the time of initiating therapy. This combined form of treatment results in "total castration"—that is, it eliminates the effect of any circulating adrenal androgens. A prospective randomized trial to determine whether this combination therapy offers any advantage over conventional therapy is currently being carried out as an intergroup study by several oncology study groups.

The use of chemotherapy for prostate cancer has been studied extensively by the National Prostatic Cancer Project. It is now felt that prostate cancer is heterogeneous and composed of cells that are both sensitive and insensitive to hormones. Hormone "failure" occurs when the hormone-insensitive cells become the predominant cells present. The goal has been to identify single agents and combinations that might prove effective against the hormone-insensitive cell population. The more active single agents that have been identified in randomized trials include methotrexate, cyclophosphamide, cisplatin and estramustine. Trials in which the use of single agents has been compared with that of two- and three-drug combinations have failed to show a statistical advantage of the use of combinations. A variety of combinations have been used, most of which include some sequence of cyclophosphamide, 5-fluorouracil, doxorubicin (adriamycin) hydrochloride, mitomycin, cisplatin or estramustine.

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Section Editor's Comment:

External beam x-irradiation and interstitial irradiation are other areas of treatment to be considered in appropriate cases.

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New Uses of Lasers in Urology

THE NEODYMIUM-YTTRIUM-ALUMINUM-GARNET (Nd-YAG), carbon dioxide and argon lasers are now being used for urologic operations. The use of the Nd-YAG laser in the treatment of bladder cancer has offered some unique advantages. The work of Hofstetter in Germany in the late 70s showed a greatly decreased recurrence rate in patients with T_1 and T_2 lesions of the bladder. His 20% recurrence rate in more than 600 patients treated has now been duplicated with a small series by both ourselves and Malloy and co-workers at the University of Pennsylvania.

Other advantages to patients have been a decreased stay in the hospital (generally, the procedure can be done on an outpatient basis or with a one-night stay), usually avoidance of the need for a catheter, ease of treatment of tumors in areas of the bladder not easily accessible with a resectoscope and avoidance of obturator reflex complications. Many patients with carcinoma of the penis, erythroplasia of Queyrat or giant condylomata of Buschke can now also be treated with the YAG laser, avoiding penile amputation. The treatment of small condylomata can be attained with either the CO_2 or YAG laser, but in patients with extremely large, bulky condylomata, the YAG laser has offered a new dimension of treat-

ment that has not been available in the past with conventional means of therapy.

The YAG laser has also been used to treat patients with interstitial cystitis and urethral stricture disease. Patients with interstitial cystitis have shown some promising results, especially those who have been refractive to all other conventional means of therapy. Unfortunately, the treatment of strictures has been the least rewarding of all of the new laser applications due to the relatively high recurrence rate seen by both Smith and ourselves.

A new field that is rapidly developing is the use of dye sensitizers such as hematoporphyrin derivative, which are concentrated in tumor cells and then, when exposed to an argon laser, cause necrosis of the tumor cells. This technique has been used with superficial skin lesions from breast carcinoma or melanoma but more recently has been used in the bladder for treating patients who have carcinoma of the bladder.

As the technology continues to improve, lasers will offer urologists in the 1980s more and exciting applications.

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Section Editor's Comment:

Endoscopic laser operation is still investigative in nature and we are eagerly waiting to learn of its full benefits and disadvantages.

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Cancer of Testis Curable

SURVIVAL PATTERNS in patients with nonseminomatous germ cell cancer of the testis have shown dramatic improvement in worldwide experience. Management changes in the past seven years have underscored the impact of more effective chemotherapeutic agents along with operative intervention. Using judicious selection of retroperitoneal node dissection and chemotherapy with cisplatin, bleomycin sulfate and vinblastine sulfate, stage B disease is virtually 100% curable. In addition, advanced or relapsed disease responds to salvage chemotherapy with more than 80% survival rates when cytoreductive operations are grossly complete and with 40% survival rates when persistent carcinoma remains.

High inguinal orchiectomy is the universal choice for initial treatment of a testicular tumor. When nonseminomatous tumor is diagnosed, clinical staging includes a computed tomographic scan of chest, mediastinum, abdomen and pelvis for detecting metastasis. Blood tests include determining α-fetoprotein and β-subunit human chorionic gonadotropin serum levels. If staging rules out extensive nodal involvement or widespread metastasis, retroperitoneal lymph node dissection may follow. If all markers are negative for tumor, some centers offer chemotherapy and surveillance alone without doing retroperitoneal lymph node dissection (Figure 1).

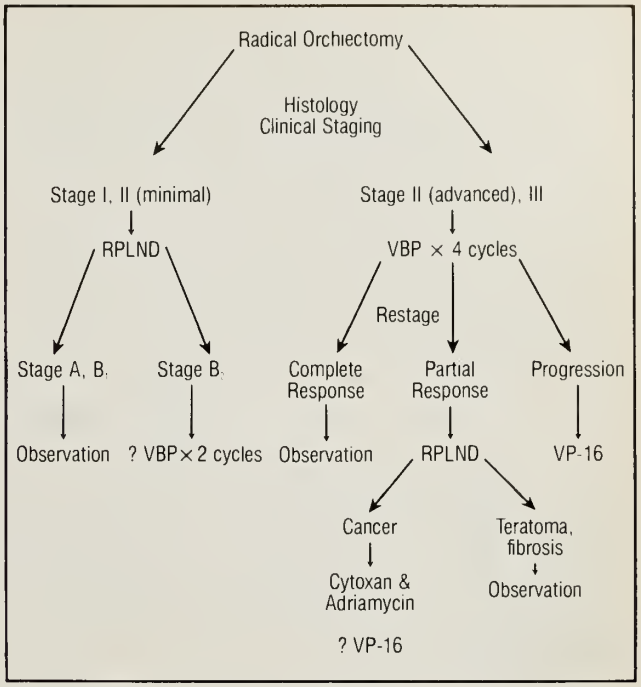

Figure 1.—Recommended plan of treatment for patients with nonseminomatous testicular cancer. RPLND = thoracicoabdominal retroperitoneal lymph node dissection; VBP = vinblastine sulfate, bleomycin sulfate and cisplatin; VP-16 = etoposide (VP-16-213)

When no (stage A) or minimal (stage B) tumor deposits are found, close observation with salvage chemotherapy of recurrences (less than 10%) is appropriate. Virtually all such patients with recurrence will respond. When extensive nodal involvement in the abdomen (stage B3) or mediastinum is present or when widely metastatic tumor (stage C) is found, triple-agent chemotherapy is initiated. Patients who respond but who still have residual lesions are subjected to surgical intervention (retroperitoneal lymph node dissection). Patients showing progression may receive adjunctive chemotherapy using other agents such as etoposide (VP-16-213). Combined patient management by a urologist and an oncologist is recommended.

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Needle Urethral-Vesical Suspensions for Stress Incontinence

SINCE PEREYRA first described the needle urethral-vesical suspension procedure for stress incontinence, modifications have provided urologists with a procedure that has a 90% or greater success rate. It eliminates the need for an open pelvic operation through a substantial abdominal incision with splitting of the abdominal wall fascia; it significantly reduces operative time and intraoperative blood loss; it significantly decreases postoperative pain and duration of hospital stay, and it allows repair of an associated cystocele, enterocele or rectocele through the same approach.

The Raz modification of the Pereyra procedure uses a transvaginal approach, passing sutures through the retropubic space with the use of a long blunt needle. These sutures are secured above the rectus fascia, requiring only a small suprapubic skin incision. Transvaginal entrance into the retropubic space completely mobilizes the bladder neck, allowing finger guidance of the needle and the use of endopelvic fascia and posterior vaginal wall substantially lateral to the urethra for the repair. In cases of urethral incompetence due to multiple procedures, a fascial sling underneath the urethra can be constructed using the same approach. This sling will increase urethral closing pressure and provide the needed bladder neck and urethral elevation.

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Infertility—Evaluation and Management

ANDROLOGY is the study of men, particularly the male reproductive system. New developments in recent years have improved andrologists' ability to evaluate, diagnose and treat cases of male infertility. A screening semen analysis is the first step in evaluating a man's fertility potential. This includes the number of sperm, their percentage of motility and the ratio of normal to abnormal forms. If abnormal, then a medical history and physical examination are in order.

Of men evaluated for infertility, 36% have a varicocele, which is due to abnormal blood flow to the testicle and can be surgically corrected. The technologic advances in microsurgery have increased the success of vasovasostomies, with about 90% having sperm present in the ejaculate. But in only 50% to 70% of cases does a pregnancy result. These differences are probably due to the duration of vas obstruction before vasovasostomy. Structures like the epididymis, which were previously inoperable, can now be readily anastomosed using an operating microscope. An alloplastic spermatocele may provide men with congenital absence of the vas a method of having children; three pregnancies have been reported. In vitro fertilization can also be done to improve fertility when male factors contribute to infertility. This requires only thousands of sperm instead of millions.

In vitro techniques using the husband's sperm can improve the ejaculate for artificial insemination. Artificial insemination with donor sperm is an alternative for those couples in whom the man is sterile and his wife would like to experience the normal sequence of pregnancy, delivery and breast feeding.

The ability to preserve sperm by freezing has revolutionized the clinical treatment of infertility. In the near future, embryo and ovum banks will be as well established as sperm banks are today.

The clinical indications for sperm banking are twofold: one, to preserve sperm for men who will be sterilized either voluntarily by vasectomy or involuntarily due to therapies that will cause irreversible damage to spermatogenesis; two, as a source of donor sperm for those couples who are barren due to male infertility that cannot be corrected. The donors are representative of many backgrounds and offer diverse physical characteristics.

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Noninvasive Evaluation of Scrotal Masses

HIGH-FREQUENCY, real-time sonography provides a nonoperative method to locate scrotal masses and to distinguish lesions requiring clinical follow-up alone. Scrotal scanning with 7.5- or 10.0-MHz high-resolution real-time ultrasound correctly identifies vascular, neoplastic, cystic or traumatic lesions of the scrotal contents.

In an infertile patient, a small varicocele may not be clinically detectable. Sonographic detection is superior to that of thermography, venography, radioisotope scanning or Doppler techniques for accuracy. Small varicoceles have the same effect on male fertility as large ones and detection defines a therapeutic approach.

Testicular rupture, although rare, is difficult to define clinically due to edema, hematoma and pain. In 30 case studies by sonography, one false-positive and no false-negatives were reported.

Although testicular torsion can be correctly diagnosed with a Doppler stethoscope and radioisotope scans, scrotal ultrasound complements these studies and also defines a nonpalpable testis.

Gray-scale sonography for accurately locating solid scrotal masses at an intratesticular or an extratesticular site has been used for some years. In addition, identification of a clinically occult testicular neoplasm, suspected by biopsy results from a metastatic site, has been reported in several series. At this time, however, scrotal sonography must be considered only confirmatory in the differential diagnosis of benign versus malignant lesions and surgical exploration is required when clinically indicated.

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Advances in Pediatric Urology

THE EFFORT of pediatric urologists to identify and correct genitourinary problems at a younger age has been furthered by several recent developments, the most provoking of which is the early diagnosis of fetal anomalies by prenatal ultrasound. Renal agenesis, hypoplasia, hydronephrosis and oligohydramnios may alert a physician to the need for early therapy. If progressive bilateral hydronephrosis with oligo-

hydramnios is found, antenatal intervention percutaneously or via an open surgical procedure or early delivery may be warranted though the risks are high. If the abnormality is unilateral or the amniotic fluid is normal, the pregnancy may be followed to term and further evaluation and treatment undertaken in the neonatal period. This promises improved salvage in the future for problems that might otherwise remain silent until severe renal damage has occurred.

Another less technical advance has been the growing appreciation for the need to thoroughly evaluate the first childhood urinary tract infection, regardless of the sex of the child. Most renal scarring from pyelonephritis has occurred by age 4 years. Before that age, immature renal papillae may contribute to intrarenal reflux, which, combined with vesicoureteral reflux of infected urine, may transform cystitis into pyelonephritis. Because a single childhood urinary tract infection has an 80% chance of recurrence, and voiding cystourethrography done on white children for infection shows reflux in 29% to 50%, the best approach to preventing recurrent pyelonephritis with its complications of hypertension, proteinuria and reduced renal function is to properly document all instances of urinary tract infection and do a diagnostic workup on those children after the first such episode.

Voiding cystourethrography or isotope cystography and excretory urography or renal ultrasound studies usually are sufficient to identify upper urinary tract anomalies, obstruction or reflux; cystoscopy is reserved for selected situations. Analysis of urine and urine culture should be considered in evaluating all febrile childhood illnesses, however transient. The goal is to identify and correct contributing causes to upper urinary tract infection and thus prevent progressive morbidity and renal damage.

On the surgical front, the impetus has been to earlier surgical procedures, often done on an outpatient basis. Electron-microscopic studies of patients with undescended testes showing deterioration beginning by age 1 year have indicated that the optimal age for orchidopexy be revised down to age 12 to 24 months. While studies evaluating the proper role for human chorionic gonadotropin or gonadotropin-releasing hormone in treating this condition are not yet complete, this hormonal manipulation should be begun by age 18 months, allowing early orchidopexy if it fails. The early promise of the gonadotropin-releasing hormone in European trials has not yet been confirmed here.

The most common type of hypospadias, a subcoronal meatus with an incomplete, dorsal-hooded foreskin, is now best treated by the meatoplasty and glanuloplasty ("MAGPI") procedure as introduced by Duckett. With advancement of the meatus onto the glans and repositioning or revising the foreskin, the procedure can easily effect an excellent cosmetic result with few complications. Often it can be done on an outpatient basis and be completed in infancy. Such procedures and timing should prevent the emotional and sexual insecurities that often accompany genital deformities in older boys.

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Section Editor's Comment:

The appropriateness of antenatal intervention is being investigated.

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Editorials

Confrontation, Competition or Cooperation

CONFRONTATION, competition and cooperation are three ways humans interact with one another when there are different views or perceptions of how best to do something. They form a sort of spectrum in which the accent shifts from the adversary to the common interests. And in any given situation one may ask where in this spectrum of confrontation, competition or cooperation can human energy (that is, intellect, time, money or strength) either of persons or groups of persons be most efficiently used? Or, to put it another way, is the focus better placed on the differences or the common interests?

Upon even superficial inspection, confrontation—with adversaries pitted against one another—is usually costly in human energy for whatever may be gained, and is always destructive. Competition can be useful if efficiency is improved, and may or may not be destructive. Cooperation is more apt to be both useful and constructive, and it can be more or less demanding of human energy. Human nature is such that in the aggregate we seem able to confront, compete and cooperate all at the same time and often in the same field of interest. There are many examples of this in business and industry. But there is much in all this that is wasteful of human energy, and of resources such as dollars as well.

In these terms it seems that there is much that is wasteful in health care in the present circumstances. Confrontation is all too prevalent, whether between physicians and patients, medical staffs and hospitals, or in court or other government interventions in health care. Competition has just recently become almost rampant with results in both the quality and costs of care that are yet to be seen. And cooperation in health care often now actually seems to be suspect by the Federal Trade Commission or the Department of Justice which enforces the anti-trust laws, particularly if the cooperation begins to show signs of being in any way efficient or effective.

All of this can only be enormously wasteful of human energy and of dollars for health care. And it can only signify a profound societal misunderstanding of the health care system, its nature and its problems of making its always-to-be-limited resources available to those who need them, when and where they need them. If the national goal of access to adequate health care of good quality for anyone who needs it is ever to be even approximately achieved, it will obviously require the most efficient uses possible of the human energy and dollar resources that are, and are to be, available for health care. Divisive confrontation and destructive competition simply have to be counterproductive to any genuine realization of the common human goals for health care, given the fiscal facts of life now and for the foreseeable future. To this small voice, no doubt crying in the wilderness, it seems that efforts toward collaboration and cooperation should be given much more of a chance than is now the case. After all, when cooperation and collaboration were more the order of the day, our health care system did produce the best health care for the most people that the world has ever seen. It seems reasonable to believe that collaboration and cooperation could be far less wasteful than the confrontation and competition we have today.

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Neurological Paraneoplastic Syndromes

THE TERM "paraneoplastic syndromes" achieved the exalted status of a specific subject heading in the *Index Medicus* five years ago, thus indicating the coming of age of another "hot topic." Neurologists should take special pride in this encomium since, in general, it was they and not oncologists who early on drew attention to these complications of cancer. In particular, we owe a special debt to a superb group of British neurological clinicians and neuropathologists, among whom Brain, Greenfield and Henson—who in the 1950s and 1960s made us aware of the remote effects of cancer on the nervous system—stand out.

Paraneoplastic syndromes are not restricted to a single organ. To name but a few examples, they may affect the skin (acanthosis nigricans maligna[1]), the kidney (minimal change glomerular disease[2]), the gastrointestinal tract (intestinal pseudo-obstruction[3]), the bone marrow (pure red cell aplasia[4]) and the upper airway (Bazex's syndrome[5]). The production of hormones, proteins and other substances by neoplastic cells may have widespread metabolic effects, such as the adrenocorticotropic hormone secretion by oat cell carcinomas producing Cushing's syndrome, the prolactin production by hypernephromas causing galactorrhea and the parathormone manufacture by squamous cell cancer of the lung resulting in hypercalcemia.[6] The thromboembolic diathesis of malignancy also can be considered a paraneoplastic syndrome.

In this issue, Palma has presented a useful summary of the paraneoplastic syndromes of the nervous system. Although each may occur in patients in whom tumors never develop, the statistical association with cancer—and sometimes with a particular type of tumor—is compelling enough to give credence to the view that in some way the neoplasm favors or facilitates the development of the neurological disorder.[7] Although the incidence of these effects on nervous tissue unrelated to metastasis is not great (approximately 10% of the neurological morbidity in patients with cancer[8]), many of them are so curious and unusual as to be unforgettable. I doubt that many clinicians will fail to recall the bizarre presentation of their first case of limbic encephalitis or cortical cerebellar degeneration which defied all attempts during life to find a cause. No one interested in this field should fail to read the poignant and instructive account by Carr[9] of the presumed effect of pulmonary Hodgkin's disease on the limbic system of his young daughter.

Palma correctly points out that one reason for clinicians to become familiar with these neurological syndromes is that they commonly precede awareness of the associated and undiscovered tumor. He suggests a few simple studies to screen

patients for the associated neoplasm. One problem in this regard is that the cancer may be so small as to defy every effort to expose its presence. In such instances, only at autopsy has a tiny breast, ovarian or pulmonary malignant lesion finally been found. Thus, there seems little correlation between the extent of a neoplasm and the severity of the neurological disease. If a cancer is found during life, therapy directed at the neoplasm itself may occasionally ameliorate the symptoms of the paraneoplastic syndrome.

The cause of these remote effects of cancer is quite perplexing. It appears likely that to look for a single cause may be too simplistic but clear openings into this mysterious relationship between tumor and host are not yet evident.[10] Simpson[11] has suggested as a possible mechanism for the induction of the myasthenic (Lambert-Eaton) syndrome, as well as other paraneoplastic events, that enzyme induction takes place at a postsynaptic site. He postulates that peptides released by cancer cells, immunoglobulins acting directly on postsynaptic membranes or immune complexes with hormonal activity may promote the activation of acetylcholinesterase and speculates that this surplus enzyme may modify brain function, possibly by destroying neurotransmitters. This would then be the obverse of the much more familiar enzyme-deficiency states.

The known secretion of hormones and other substances previously alluded to has been invoked by analogy for the pathogenesis of some of the neurological paraneoplastic syndromes, but as yet there is no firm evidence for this speculation. Good data implicating immunological factors are sparse also. In a case of cortical cerebellar degeneration associated with ovarian carcinoma, Steven and co-workers[12] found weak binding of cerebrospinal fluid immunoglobulin to multiple neural components, while others have found serum antibodies to Purkinje cells in similar patients.[13] These antibodies are alleged to have appeared before the onset of clinical signs of the cerebellar degeneration. However, there is as yet no proof of a cause and effect relationship, it is unclear just what the antigen(s) is and the immunoglobulins may simply be epiphenomena. The role of nutritional and toxic factors is always raised in disorders of unknown cause but no hard evidence exists to credit such hypothetic factors with an etiologic role. Recently, overproduction of prostaglandins has been suggested as a mediator of some of the paraneoplastic syndromes.[14]

Neuropathologists have long been impressed with the inflammatory changes noted in the neural tissue of patients with paraneoplastic encephalomyelitis, and the possibility of a viral cause has been discussed frequently. The immunodeficient state of cancer patients adds some weight to this hypothesis, as exemplified by the important identification of the etiologic role of papovaviruses in the production of progressive multifocal leukoencephalopathy. This disorder, not discussed in Palma's article although it was the initial topic considered in the first conference on the neurological aspects of the remote effects of cancer,[15] is the first demyelinating disease proved to be related to a virus and is most frequently found in association with Hodgkin's disease and other lymphomas.

Another unusual neuropathologic aspect of the paraneoplastic syndromes is that sometimes there is juxtaposition of two or more different types of pathologic disorders in the same patient. For example, cerebellar degeneration, bulbar encephalitis and peripheral neuropathy have been found in a patient four years after a radical mastectomy in the absence of any recurrent neoplasm at autopsy.[16] In addition, while most of the cortical cerebellar cases have had degenerative histopathologic changes primarily, some apparently identical patients have had a predominance of inflammatory changes in the cerebellum. Clinically, several paraneoplastic syndromes may occur in the same patient, giving rise to a confusing combination of neurological signs. Halperin and associates[16] suggest the possibility that a common etiologic event may trigger independent pathologic processes, but no explanatory mechanism is offered.

Among the strangest of these syndromes are the rare necrotic myelopathies, both acute and subacute. While metabolic or other factors have been invoked as hypothetic causes, careful examination of the state of the spinal arteries from their origin at the aorta to their termination in the spinal cord has not been done, to my knowledge. It may be that necrotic myelopathy is a special case of thrombosis of pertinent arteries in hypercoagulable cancer patients.

Some of the paraneoplastic syndromes described by Palma, such as polymyositis, the myasthenic syndrome and the peripheral neuropathies, are relatively easy to diagnose while others, such as different types of encephalomyelitis and the cerebellar degenerations, may be quite difficult. The encephalitic forms can have an insidious onset and may suggest primary psychiatric syndromes—such as depression or anxiety—or dementing illnesses—such as Alzheimer's disease. The cerebellar degenerations are presumed to have immunoglobulin changes in the cerebrospinal fluid, since reports from the past noted abnormalities in the now nearly forgotten colloidal gold test. Not enough data have yet been reported to clearly indicate whether these abnormalities, such as an increase in oligoclonal bands and IgG, are reflected in contemporary tests.

We are likely to see more cases of these paraneoplastic syndromes in the future, as patients with cancer live longer and thus their nervous systems are exposed for longer periods to what are often literally malignant influences. New clinical and pathologic syndromes are likely to be described as clinicians and pathologists recognize deviations from the usual. The unraveling of the enigma of the paraneoplastic syndromes will be an important step towards a more complete understanding of the biology of cancer.

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Doctors Versus Lawyers

A Crucial Battle Has Been Joined in California

AT A SPECIAL SESSION in 1975 the California legislature enacted and the governor signed the Medical Injury Compensation Reform Act (MICRA). This was and is the strongest tort reform legislation in the nation. During the ensuing decade most of the key provisions were tested in the courts, and just recently the last and most important of them were upheld by the California Supreme Court. The key provisions that were upheld include periodic payment of awards, elimination of third party lien claims, limits on attorneys' contingency fees, a $250,000 limit on noneconomic (pain and suffering) losses and modification of the "collateral source" rule. Many attorneys had believed this 1975 law would be declared unconstitutional, either in whole or in part. When finally it was not, first there was dismay and then a rather intense reaction by the trial lawyers, possibly because it affects their pocketbooks, in some cases maybe even retroactively. The California Medical Association worked hard and successfully for the passage of this law in 1975, and now in 1985 the California Trial Lawyers Association is committed to work hard for a bill (SB 520) that would repeal significant provisions of the 1975 law, and there is even talk of a ballot initiative for a constitutional amendment to negate MICRA. The California Medical Association will again work hard, this time to retain the law in the face of what is certain to be formidable opposition. Needless to say, a crucial battle has been joined in California. It is doctors versus lawyers over an issue that is important to both, as well as to patients (whether injured or not) and to the public.

This confrontation pits two learned professions against each other and also tests their basic values. In our American tradition the law thrives on an adversary approach with the outcome decided in a courtroom contest among attorneys who seek to influence a judge or jury to their particular view of a case, while medicine strives for a more objective approach to seek out the truth and works together with all parties at interest as it tries to find what is most likely the fact or the truth. These two approaches are quite different, as seems apparent in the differing attitudes of lawyers and physicians toward medical injuries. The one wants to find someone to blame and to collect as much compensation as possible (from as deep a pocket as possible), while the other wants to find out what went wrong and to learn as much as can be learned from an unfortunate incident in order to lessen the likelihood of damage to others in the future. However, physicians agree that where genuine malpractice or gross negligence has occurred, the unfortunate victim is entitled to reasonable compensation.

Both our medical system and our legal system permeate almost every facet of our society, and sooner or later affect almost every person. It is therefore significant that they approach things differently. Both systems are also very expensive. No one really knows what the cost of the legal system is with all its laws, regulations and expensive litigation. It must be enormous. And of course the public ultimately pays the cost of both systems and it is in the interest of the public that the one be as cost efficient as the other. This being the case, it would appear that the cost to the public of what some might call the "liability rip-off" is what is really at stake in this battle now being entered into between doctors and lawyers in California. Costly litigation and often excessive compensation for personal injury is a growing national problem. It happened to come sharply into focus in California in 1975 when the availability of professional liability insurance for physicians was threatened because of skyrocketing losses by insurance carriers. MICRA, as passed in 1975, made it possible for insurance carriers to remain in the field and even for new carriers to enter it. Now in 1985 yet another malpractice crisis is predicted by the experts. This time many physicians will simply not be able to pay the ever rising premiums, particularly in certain specialties, and will have to withdraw from very high risk practices. This is actually already happening, and many more will have to do this as their risk increases and their incomes become restricted as a result of regulatory restraints and some of the newer market forces. It is likely that the economic base of the nation's physicians is simply not going to be strong enough to pay the cost of the growing number and size of the medical malpractice actions and the attendant litigation. It would be crass here to do more than just mention that all of this of course profits the lawyers, and the trial lawyers particularly.

Clearly this is no time to repeal or negate the strongest tort reform law in the nation. Much more is at stake than the pocketbooks of physicians or even those of trial lawyers. Tort reform is essential for the health and well being of all of society, which much too soon may be no better able to pay for all these litigious excesses than are physicians today. It is time to move forward and not backward in dealing with this issue. It also is worth noting that this battle, and the probably many more to come, will be fought on the lawyers' turf and according to their rules of the game. It is to be hoped that the outcome will not benefit just lawyers or physicians, but rather will benefit the society both professions are here to serve, and from whose pockets (some deep and some not so deep) ultimately must come not only the cost of litigation, but the often seemingly unconscionable awards as well.

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Case Reports

Multifocal Eosinophilic Granuloma With a Pituitary Stalk Lesion

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DURING THE PAST 90 years interest in the clinical and pathological disorder variably referred to as eosinophilic granuloma (unifocal and multifocal), Hand-Schüller-Christian disease, Letterer-Siwe disease or histiocytosis X has been increasing. In the past 20 years more than 500 papers have been written in all areas of medicine describing various clinical states and syndromes in attempts to clarify the existence of this fascinating disorder.

We report the case of a woman who had involvement of lungs, bone and pituitary gland, which are features commonly seen in multifocal eosinophilic granuloma, the last two being commonly referred to as part of a triad of Hand-Schüller-Christian disease.

Involvement of the lungs in our patient is somewhat atypical in its relentless progression to the extent of being life threatening.

Report of a Case

The patient, a 44-year-old woman, first presented to the outpatient department at Sunnybrook Medical Centre (Toronto) in February 1974 complaining of fever and dry cough. Her medical history was significant only for spontaneous pneumothorax some six months earlier. At that time her chest roentgenogram was normal except for the finding of pneumothorax, which required no treatment. On initial visit her chest x-ray film showed a reticular interstitial pattern in both upper lobes. A month later she had swelling over the right seventh to ninth posterior ribs with no preceding history of trauma. A chest x-ray film showed interstitial fibrosis but no rib lesions. The patient was admitted to hospital in April 1974 and a biopsy of the lung was done, which was diagnostic of eosinophilic granuloma. The bone scan at this time was normal. A regimen of prednisone, 60 mg a day, was started, with subsequent improvement in her condition and clearing on chest x-ray film. In July 1974 the prednisone dosage was decreased to 10 mg on alternate days.

She was seen again in March and December 1975 when pulmonary function tests were done. These showed a total lung capacity of 6.8 liters, impaired gas transfer and mildly reduced flow rates. In March 1976 repeat pulmonary function tests showed normal lung volume but further impaired diffusion capacity and flow rates.

In December 1976 a regimen of vinblastine sulfate, 10 mg a week given intravenously, was started because of slowly deteriorating pulmonary function. The vinblastine therapy was continued until 1978 and during this time her pulmonary function test results remained stable.

From 1978 to 1980, however, her pulmonary function tests showed a slow deterioration. Symptomatically she became more short of breath and she had two visits to an emergency department for acute bronchospasm.

In October 1980 she was referred for endocrinologic assessment because of polydipsia (more than 20 glasses of cold water per day), polyuria and nocturia for five weeks. No symptoms of dysuria were disclosed and her menstrual periods were regular. On examination there was no cyanosis or clubbing, visual fields were normal and there were bilateral inspiratory and expiratory rhonchi. No galactorrhea, lymphadenopathy or hepatosplenomegaly was found. Her plasma glucose level and kidney function tests were normal.

A fluid deprivation test was then done, the results of which are summarized in Table 1. She was felt to have partial central diabetes insipidus and was treated with a regimen of chlorpropamide, 125 mg given twice a day, with a good response. The chlorpropamide therapy was subsequently replaced by desmopressin acetate. The skull x-ray films, computed tomographic (CT) scan of the head and bone scan were all normal. An anterior pituitary stimulation test in the form of a double bolus containing thyrotropin-releasing hormone (TRH) and gonadotropin-releasing hormone was also done with results shown in Table 2. There was a mild elevation in the basal level of prolactin but an adequate response to TRH was observed. The basal levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) were normal and the response to gonadotropin-releasing hormone was greater than usually observed. The basal thyrotropin level was normal and there was normal response to TRH.

Until the end of 1981 the patient was doing relatively well, although there was a slowly progressive shortness of breath.

TABLE 1.—*Fluid Deprivation Test, November 1980, in a Woman With Multifocal Eosinophilic Granuloma*

Values	Time: Beginning of Test	Time: After 7 H	Time: 1 H Following Antidiuretic Hormone*
Weight (kg)	81.4	79.4	79.2
Serum sodium (mEq/liter)	142.0	149.0	150.0
Serum osmolality (mosm/kg)	286.0	296.0	301.0
Urine osmolality (mosm/kg water)	227.0	209.0	391.0
Urine specific gravity (total solids meter)	1.009	1.005	1.011

*Vasopressin (Pitressin), 5 U, was given subcutaneously

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ABBREVIATIONS USED IN TEXT

CT = computed tomography
FEV_1 = forced expiratory volume in one second
FSH = follicle-stimulating hormone
FVC = forced vital capacity
LH = luteinizing hormone
TRH = thyrotropin-releasing hormone

In December 1981 she complained of fullness in her right ear. Although on examination there was no abnormality, a nuclear bone scan showed an abnormal reaction in the right temporal bone. The alkaline phosphatase level was increased at 494 IU per liter (normal, 30 to 90). Tomograms of the right temporal bone showed abnormal thickening of the mucosal lining of the mastoid air cells but no boney destruction was evident. In May 1982 the patient had right corticomastoidectomy and right myringotomy. Intraoperatively a soft tissue mass invading the bone was noted. Pathologic features of the lesion were consistent with a chronic nonspecific inflammatory process. In September 1982 a bone scan was repeated and although there was no change in the right temporal bone, involvement of the left temporal bone was now evident.

In November 1982, after seven months of amenorrhea, provocative testing of the anterior pituitary gland was done (Table 2). The plasma estradiol level was 6.4 mg per dl (normal, 4 to 35), thyroid function tests were normal and the patient was on a regimen of prednisone, 10 mg on alternate days. The basal prolactin level was twice that noted in 1980.

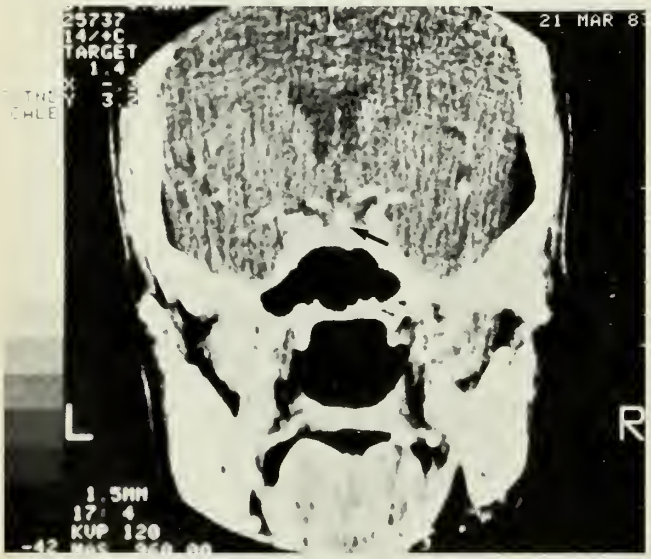

Figure 1.—Computed tomographic scan showing a mass lesion in the region of the pituitary stalk **(arrow).**

There was, however, still a good response to TRH. The basal levels of LH and FSH were lower than in 1980 and the response to gonadotropin-releasing hormone was much reduced, although the LH response was still adequate. The baseline thyrotropin level was similar to previous values, but the response to TRH was lower than previously recorded.

In February 1983 she was still working full time as a stenographer. She continued to be amenorrheic and now had galactorrhea. Pulmonary function tests showed a restricted lung volume (total lung capacity, 4 liters; forced vital capacity [FVC], 2.4 liters; residual volume, 1.5 liters; forced expiratory volume in one second [FEV_1], 2.1 liters, with a ratio of FEV_1/FVC of 87.5%) with severely impaired diffusion but normal air flow. The LH and FSH levels were less than 3 mIU per liter and the prolactin level was greatly elevated at 102 ng/ml. In March 1983 a CT scan of the head showed a small enhancing mass in the region of the pituitary stalk (Figure 1). Ophthalmologic examination showed full visual fields and early papilledema.

Following the above investigations, the patient was treated with radiation therapy to the skull and pituitary gland consisting of 600 rads in four fractions. Cor pulmonale subsequently developed and she requires oxygen 18 hours per day.

Figure 2.—A chest x-ray film (taken December 20, 1983) showing extensive interstitial fibrosis.

TABLE 2.—*Double-Bolus* Pituitary Function Test in a Woman With Multifocal Eosinophilic Granuloma*

Hormone Levels	November 1980 Baseline	20 min	40 min	60 min	November 1982 Baseline	20 min	40 min	60 min
Thyrotropin (μU/ml)	4.4	18.3	17.2	14.8	3.6	7.4	7.9	6.5
Prolactin (ng/ml)	33.0	74.0	71.0	68.0	67.0	119.0	102.0	88.0
LH mIU/ml	34.0	>100.0	>100.0	>100.0	7.0	20.0	16.0	16.0
FSH mIU/ml	21.0	46.0	35.0	90.0	11.0	3.0	13.0	13.0

FSH=follicle-stimulating hormone, LH=luteinizing hormone

*The double bolus contained 200 μg of thyrotropin-releasing hormone and 100 μg of gonadotropin-releasing hormone given intravenously.

Her most recent chest x-ray film (December 20, 1983) was unchanged from the previous one (Figure 2).

Discussion

In summary, this patient presented as a 44-year-old woman with a ten-year history of multifocal eosinophilic granuloma. There was initial involvement of the lungs with subsequent development of pituitary and boney lesions. The age of the patient and the progressive course of the disease are uncommon in the presentation of eosinophilic granuloma.

It is interesting that our patient had a pneumothorax. The association of diabetes insipidus and pneumothorax in multifocal eosinophilic granuloma has previously been noted in the literature. Lewis[1] reviewed the clinical features of 75 patients diagnosed as having eosinophilic granuloma by lung biopsy. Six of seven patients with diabetes insipidus also had pneumothorax. However, Friedman and co-workers,[2] in their discussion of 60 cases with pulmonary involvement, noted that of five patients who had diabetes insipidus, none had pneumothorax. The authors also pointed out that further systemic involvement was unusual (none in their series) following presentation with primary pulmonary lesions.

Pulmonary disease in our patient appeared to be characteristic of that in eosinophilic granuloma. Evaluation of pulmonary function showed a pattern of decreased diffusion capacity and restricted lung volumes. There was not reduction in air flow.

Eosinophilic granuloma of the lung in our patient was treated initially with a regimen of prednisone, 60 mg a day, with objective and subjective improvement. However, low-dose therapy with 10 mg of prednisone on alternate days seemed to give only subjective relief of the symptoms with continuous progression of pulmonary disease. It is possible that in the absence of the steroid treatment, a more rapid course of the disease would have taken place.

A similar statement could be made as far as treatment with vinblastine in our patient. Over the period of time that vinblastine was administered there was no deterioration as shown by pulmonary function test results. However, neither was there any improvement. Whether this pattern was part of the natural course of the disease in this particular patient is unknown.

Evidence of hypothalamic-pituitary axis involvement became apparent in our patient about a year and a half after the initial presentation. At that time dysfunction of the posterior pituitary was evident based on the results of the fluid deprivation test. Diabetes insipidus is the most common endocrinopathy of multifocal eosinophilic granuloma and is well documented in the literature.[3-5] It has also been pointed out in the literature that primary lesions of the anterior pituitary are quite uncommon and any abnormality of function can be ascribed to lesions in the hypothalamus.[6-8]

There was an increase in the basal level of prolactin and a decrease in both the basal gonadotropin levels and their response to gonadotropin-releasing hormone stimulation with the development of secondary amenorrhea and galactorrhea. These abnormalities are probably due to the pituitary stalk lesion observed by computed tomography.

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Kaposi's Sarcoma Presenting as Homogeneous Pulmonary Infiltrates in a Patient With Acquired Immunodeficiency Syndrome

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AGGRESSIVE KAPOSI'S SARCOMA is a well-described occurrence in patients with acquired immunodeficiency syndrome.[1] Even when the disease is widely disseminated, however, the chest radiograph is usually normal.[2] Although Kaposi's sarcoma has been reported in the lung,[3] we report the first case of Kaposi's sarcoma in which the initial clinical manifestation was a rapidly progressive, homogeneous pulmonary infiltrate. This case stresses the importance of considering Kaposi's sarcoma in the differential diagnosis of pulmonary infiltrates, even in the absence of other visceral or dermatologic manifestations.

Report of a Case

The patient, a 30-year-old homosexual man, was admitted to the University of California Irvine Medical Center with complaints of malaise, weight loss, alopecia and bright red blood per rectum for two months. A test for hepatitis B surface antigen was positive. The patient had herpes proctitis (confirmed by clinical diagnosis and by culture results) and *Giardia lamblia* enteritis. A chest roentgenogram showed infiltrates involving the left upper and lower lobes and the right midlung field. A diagnosis of *Pneumocystis carinii* pneumonia was made by bronchoscopic biopsy and trimethoprim-sulfamethoxazole therapy was initiated. Erythema multiforme developed, but resolved when the trimethoprim-sulfamethoxazole regimen was discontinued. Pentami-

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dine therapy was begun and continued for a total of 21 days with subsequent pronounced improvement as shown by the chest roentgenogram and by the patient's physical condition. Results of immunologic studies were consistent with a diagnosis of acquired immunodeficiency syndrome. The patient was discharged.

Three weeks later he returned to hospital with fever, chills and cough productive of yellow sputum. At this time he appeared cachectic, but was afebrile. A careful physical examination showed no skin lesions and only a few shotty, small, anterior cervical lymph nodes. Lungs were clear to auscultation; the abdomen was soft, nontender and without hepatosplenomegaly. A rectal examination showed scarring in areas of previous proctitis. The stool was brown and a stool specimen was positive for trace amounts of occult blood. A chest roentgenogram showed a residual patchy infiltrate involving primarily the left upper lobe.

The patient's hospital course was complicated by low-grade fevers with occasional fever spikes. All cultures were negative. Sputum smears and bronchoscopy were nondiagnostic. A bone marrow specimen was considered normal. At six weeks, blood, sputum and marrow cultures became positive for *Mycobacterium intracellulare avium* and antimycobacterial therapy was initiated. Rectal bleeding developed and a sigmoidoscopic examination showed a rectal fissure and old scarring. Cultures were negative for herpes. The patient's mental state deteriorated gradually although his physical state was stable until the 58th hospital day, when his temperature abruptly reached 40°C (104°F) and he had diffuse rhonchi, increased sputum and mild respiratory distress. A chest roentgenogram taken at this time showed new, diffuse alveolar and interstitial infiltrates involving both lung fields, radiographically a more extensive but somewhat similar picture to the earlier findings of *Pneumocystis* (Figure 1). Consideration was given to simply initiating pentamidine therapy. However, specimens taken by bronchoscopy and stained showed no *Pneumocystis* or other pathogens. Results of open-lung biopsy showed only Kaposi's sarcoma. Eight days later, the patient died.

Autopsy showed Kaposi's sarcoma involving the rectum and retroperitoneal and mediastinal lymph nodes with diffuse involvement of the lungs (Figures 2 and 3). Periodic acid-Schiff stains, Giemsa stains, hematoxylin and eosin stains, methenamine silver stains, routine cultures, fungal cultures and mycobacterial cultures were done. The results of all studies were negative except that at eight weeks the lung autopsy specimen grew a few colonies of *M avium*.

Discussion

Kaposi's sarcoma in homosexual patients with acquired immunodeficiency syndrome is extremely aggressive[4] and can involve virtually any organ system.[1] The lung, however, is rarely involved.[2] Reports of lung involvement are nearly always of an indolent reticular-nodular infiltrate noted in the presence of sarcoma of the skin or lymph nodes.[5] Kornfeld and Axelrod have reported a case of acquired immunodeficiency syndrome with nodular, interstitial infiltrates from Kaposi's sarcoma: this patient had no other obvious sarcoma elsewhere.[3] They described the case of a patient with a subacute course in whom *P carinii* pneumonia developed after several months and who died thereafter of respiratory failure.

The composite, therefore, of a patient who has acquired immunodeficiency syndrome with pulmonary Kaposi's sarcoma is a homosexual man who has obvious sarcoma in the skin, lymph nodes or other viscera, and in whom hilar adenopathy then develops with nodular or linear infiltrates. These patients frequently have or will go on to have concomi-

Figure 1.—Roentgenogram of patient's chest taken just before open-lung biopsy, showing new diffuse alveolar and interstitial infiltrates.

Figure 2.—Gross lung specimen taken at autopsy.

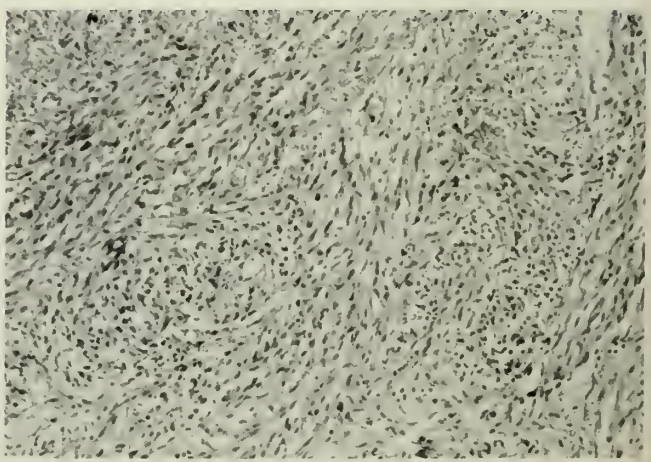

Figure 3.—Tumor growing into alveolar walls (× 120).

tant pulmonary infection with any of a variety of agents including *P carinii*, cytomegalovirus, *Cryptococcus*, *Toxoplasma*, *Aspergillus*, *Candida*, *Legionella*, *Histoplasma* and *Petriellidium boydii*.[1,5]

Our patient is unique in several respects. Most important, this is the first report of pulmonary Kaposi's sarcoma presenting as an aggressive, alveolar infiltrate progressing rapidly to respiratory failure and death. Extensive pathologic evaluation and many cultures were done. The only evidence of other pathologic features was the growth of a few colonies of *M avium*. We feel strongly that the infiltrate was due to Kaposi's sarcoma and not *M avium* for the following reasons: The patient was being treated with five antimycobacterial drugs for *M avium*, which had previously been identified in the central nervous system, and the infiltrate occurred very rapidly; the acid-fast bacilli stains were entirely negative on both biopsy and autopsy specimens, and the biopsy specimens showed extensive tumor invasion of the parenchyma and possible disruption of the alveolar wall.

This case also serves to remind clinicians that Kaposi's sarcoma can present first in the lung. At autopsy some retroperitoneal and mediastinal nodal involvement was found that was not apparent clinically. In addition, the rectal involvement was attributed to scarred herpetic proctitis and therefore a connection with Kaposi's sarcoma was overlooked.

When rapidly progressive homogeneous infiltrates appear in patients with acquired immunodeficiency syndrome, the most common cause is *P carinii*.[5] However, all of the organisms mentioned above must be considered. Although Kaposi's sarcoma generally causes indolent, nodular infiltrates in patients whose sarcoma is apparent in other organs, our case suggests that Kaposi's sarcoma should also be included as a possible aggressive pneumonitis. The recognition of this phenomenon is important for at least two reasons. First, because, as in our patient and in others,[6] a clinician may consider administering inappropriate antibacterial therapy to a patient; and, second, because aggressive chemotherapeutic regimens may prove at least partially effective in the treatment of Kaposi's sarcoma.[4]

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Correspondence

The Editorial Board will be pleased to receive and consider for publication correspondence containing information of interest to physicians or commenting on issues of the day. Letters ordinarily should not exceed 600 words, and must be typewritten, double-spaced and submitted in duplicate (the original typescript and one copy). Authors will be given an opportunity to review any substantial editing or abridgement before publication.

Management of Stroke

TO THE EDITOR: I am writing regarding the January Medical Staff Conference, "Controversies in the Medical Management of Stroke,"[1] by Michael E. Charness, MD.

Wings was an appealing and insightful play about the effects of aphasic stroke upon a vibrant woman, and Geschwind's excellent review[2] of this play and of the consequences of stroke was both instructive and insightful. Charness's lucid and timely description of what we know and do not know about the medical management of stroke struck me similarly. Yet both Geschwind and Charness have failed to emphasize what is, in my view, one of the most important issues in patients who have suffered a completed stroke—the diagnosis and correction of problems which *led* to the stroke in the first place.

Charness's emphasis upon cardiogenic emboli notwithstanding, the majority of patients who suffer embolic cerebral infarction do so because of atheromatous involvement of the carotid bifurcation. This is generally on the basis of embolization of platelet-fibrin thrombi from ulcerative plaques at this extracranial site. While cardiac problems—myocardial infarction, congestive heart failure, arrhythmias—remain the leading overall cause of death in patients with cerebrovascular disease, the most prominent cause of death in stroke victims for the first five years after their cerebrovascular accident is, in fact, recurrent stroke.[3] Stroke victims' risk of recurrent stroke may be as high as 50% in the subsequent five years.[3,4] While these patients are being anticoagulated to diminish their chances of immediate recurrent stroke, it seems prudent to pursue an aggressive diagnostic approach, including contrast arteriography to delineate the presence of an extracranial lesion. A high-grade stenosis at the carotid bifurcation might be found, for example, or a complex ulcerative plaque—surgical relief of which might reduce *that* risk factor as a cause of recurrent stroke.

To be fair, stroke victims undergoing subsequent carotid operation are at higher risk for perioperative complications, and at least one analysis[5] has suggested that this increased risk of perioperative stroke and death essentially negates any benefit to be obtained by carotid endarterectomy. Other studies,[6] however, appear strongly to support the principle that expert operative treatment of extracranial carotid lesions in well-selected patients can be of substantial value in reducing the rate of recurrent stroke and death in stroke victims.

In short, to Charness's elegant discussion of the role of various pharmacologic manipulations in victims of acute stroke I would add a plea for early and aggressive diagnostic evaluation in search of operable extracranial vascular lesions in these high-risk patients.

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Type II Diabetes Mellitus

TO THE EDITOR: After the review "Pathogenesis of Impaired Glucose Tolerance and Type II Diabetes Mellitus—Current Status"[1] was accepted for publication, the Mayo Clinic group published a report updating their experience in patients with impaired glucose tolerance and type II diabetes (which they do not separate). In their first paper,[2] in which they studied ten patients with a mean fasting plasma glucose concentration of 182 mg per dl, the following were found: (1) decreased insulin binding, (2) a shift of the dose-response curve to extracellular insulin concentrations to the right (decreased sensitivity), (3) normal maximal responses (normal responsiveness) and (4) a normal dose-response curve to the amount of bound insulin (normal coupling between insulin binding and the effect of the bound insulin). Hence, they concluded that the mechanism of insulin antagonism in these patients was due to a receptor defect.

In their second report,[3] they added seven patients to their series, the effect of which was to change their results and conclusions. The mean fasting plasma glucose concentration in these 17 patients was 178 mg per dl so that the degree of abnormal carbohydrate metabolism did not change by adding these new patients. However, when the results of all 17 patients were analyzed, the following were found: (1) decreased insulin binding (which the authors ascribed to down regulation), (2) decreased sensitivity, (3) decreased responsiveness

and (4) impaired coupling between insulin binding and action. Hence, they now conclude that the mechanism of insulin antagonism in these patients is primarily due to a postreceptor defect.

These more recent data shift the evidence even more strongly to favor the view that a postreceptor defect characterizes patients with even mild type II diabetes mellitus.

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Cinnamon Oil Burn

To the Editor: Recently an 11-year-old boy, a sixth grade student of apparently normal intelligence, presented at the University of New Mexico pediatrics clinic with a 10 by 12 cm second degree burn on his posterior thigh. This blistered area was surrounded by a 3 to 4 cm first degree burn. The injury was the result of a cinnamon oil spill from a broken vial in his rear pants pocket. The area had remained unwashed for 48 hours, and smelled strongly of cinnamon.

In reviewing the literature and contacting Poisindex Information System, I was able to find no previous report of such an incident. It has long been known that cinnamon oil contains many irritants, cinnamaldehyde being the most strongly implicated. The oil is known to irritate mucous membranes, skin and gastrointestinal tract, as well as cause hypersensitivity reactions.

The fact that it can also burn under certain circumstances may be of importance in the Southwest. It is a common practice among school children in this part of America to soak toothpicks in cinnamon oil obtainable from drugstores and supermarkets. The toothpicks are then chewed for the flavor.

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Protective Helmets for Infants and Children on Bicycles

To the Editor: The correspondence from Drs James, Buchta and Stein[1] in the March issue draws proper conclusions from improper data. They point out that 78% of bicycle fatalities occur in children but fail to indicate what percentage of bicycle riders are children.

Their plea is for the use of specially designed helmets that protect infants and toddlers (one must presume the child to be riding behind a parent in an infant seat). However, they gave no statistics concerning the scope of the problem in this population or even if there is a problem in this population.

The statements presented in the last paragraph (excluding the last sentence) seem completely unrelated to the subject suggested by the title.

I laud efforts by those who encourage bicyclists (of all ages) to wear protective head gear and congratulate Bell Helmet, Inc, Norwalk, Calif, for designing and producing helmets for infants and small children, but I think that statistics presented to support a claim in medical literature should be related to that claim.

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REFERENCE

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* * *

Dr James Replies

To the Editor: We take note of the correspondence of Dr Michael T. Long in reference to the conclusions of the information on protective helmets for infants and children. Dr Long correctly points out that we did not break down the percentage of bicycle riders that are children. It would be very advantageous to have these data, but they are not available to my knowledge. I also wholeheartedly agree that it would be more appropriate to include statistics on the subgroups of the various populations and the types of injuries suffered. Unfortunately, once more, the data are not available.

We do know that the most common cause of hospital admission and the largest expense of health care in pediatrics is trauma. The thrust of our presentation was to make the primary care physicians caring for children (and the families who request the care) aware that there is a protective device for a child's cranium that was not previously available.

I wish to laud the efforts of two concerned pediatricians, Dr Buchta and Dr Stein, in cooperating with us and with the manufacturer in trying to make the general population and physicians aware that this is one preventive element within their reach. As always, in trauma, prevention should be our major objective.

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The True Role of Physicians

To the Editor: I wish to commend you for your editorial comments in both the February and March issues.[1-3] Your remarks present, I believe, a perspective from which we can take a broader view of our obligations to our patients and to society. Further and properly, I submit, your remarks aim beyond our one-on-one physician-patient relationships and have broad bioethical implications that potentially could not only dispel the "stereotype" of organized medicine but also contribute to efforts toward a safer, peaceful planet. This will not be an easy task, for despite the AMA survey that you reported, my own experience over the years convinces me that the self-serving image of professional associations is a widely perceived one. However, I feel very strongly that the effort will be worthwhile, and that at this particular moment it is much needed. As you so correctly point out, "real power" does not lie with organized medicine, but with society. Despite pressures from government, the media and special interests, if we fulfull our obligations to provide high quality care that is accessible to all, and affordable, then society, the

ultimate arbiters, will not allow the degradation of that kind of service.

That being the stake, I would suggest that all efforts toward influencing the "external environment . . . of evolving patient care and social change affecting medicine" would be worthwhile.

Among these external factors that I can quickly enumerate are the following:

- The danger of nuclear war;
- The costs of an escalating arms race, which not only buy us no security but rob us of the wealth we need to attack health-related problems in society (worldwide expenditures for military purposes for only *four days* would supply enough funds to wipe out malaria, the world's primary cause of morbidity);
- The threatened cuts in services for education, research, child and elder care, and the like.

I noted with considerable pleasure that at the recent meeting of the California Medical Association (CMA) in San Diego, a constitutional amendment was proposed, extending CMA's purpose to include not only the science and art of medicine but also "the care and *well-being* of patients." I believe that this amendment would most certainly obligate CMA members to be very much concerned with the above items.

I also noted an effort to finance a "CMA statewide public information program to enhance the public perception of the physician as the patient's advocate and to improve organized medicine's image." Should such a program *focus* on some of these "external" factors, the dividends could be immense, in my view. However, should the program be more internally directed and possible of interpretation as self-serving, then the investment will be a poor one.

Finally, a word of caution about your reference to the "competence of the medical profession to accomplish" its goals in external purpose. Too often in the past have I experienced recourse to this "lack of competence" (or expertise) as an excuse for inaction. Need one be an "expert" to realize that more than 50,000 nuclear warheads constitute a grave threat to the "well-being" of our patients and society?

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* * *

To the Editor: This is in response to the March editorial "Concerning Physicians' Responsibilities to Patients and to Society."[1] All physicians will agree that the first responsibility of a physician is to his or her patient. Unfortunately, however, modern society in its evolution is attempting to make physicians the scapegoat of its own political and bureaucratic negligence. Society today demands so much of physicians that many intelligent and conscientious practitioners have left these professional ranks. Your brief summary touches only a few of these present-day problems and I feel there should be a restatement of some of these at least.

(1) Physicians came before licenses by society. The physicians' code as stated by Hippocrates is the true badge of the profession and its principles will outlive all of us. A physician's duty is to her or his patient who is truly ill, not to those persons who feign illness or insult to benefit from what a generous society has to offer. A physician is not the servant of society but of the human being who is sick.

(2) The code of the physician demands maximum skill and for this training is required. The physician pays for this by dedication and the creation of her or his ability by a long educational process. Remuneration for this service must equal or exceed those of lesser training requirements and render a standard of living that is adequate. Entrepreneurs should never be allowed to market the skill of physicians; entrepreneurs will serve their pocketbooks first. Their goals can never take into account the fundamental dedication and generosity of physicians.

(3) Society, through better education and selection of its politicians, should provide better protection for dedicated physicians. Malpractice costs and fears have driven many out of the physician ranks. The cost of practice should not be prohibitive and has already led to extremely high fees. Political and legal philosophy and practice today is predatory and there should be published professional standards by which society can grade and evaluate its lawyers or governmental representatives.

(4) Physicians must not be held responsible for today's health care costs. It is obvious that the plentiful governmental dollars are being chased more by paraprofessional and health-care salesmen than by dedicated physicians. If society does not listen to those who have the courage to speak out, it will know the agony of further costly experience. Private insurance company management through established companies who have industrial medical experience could solve many of today's problems.

(5) Last, the medical profession should seek to hone once again its skills in diagnosis, care of the sick and monitoring of its own standards rather than compete for a position before television cameras. The universities should rely less on government handouts and strive for a stronger but better organized nucleus of professional teaching and responsibility. The entire medical profession cannot be all things to all people but it can be responsible to itself and the sick and not to the whims of a badly managed society.

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Commentary

'Baby Doe'—A Medical Ethical Issue

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Medical-ethical decision making is evolving under strenuous new pressures and national public exposure. The doctor-patient relationship, at the same time, is being changed and eroded. The "Baby Doe" issue spotlights a current focus for ethical debate and radiates far-reaching effects.

Who Was 'Baby Doe'?

Baby Doe was born in April 1982 with Down's syndrome, a tracheoesophageal fistula and esophageal atresia. The obstetrician, himself a parent of a child with Down's syndrome, believed that the burden of the Down's syndrome handicap weighed against surgical corrective treatment of the atresia and fistula and so counseled the family.[1] The family physician and pediatrician urged that surgical treatment was both feasible and likely to be highly successful and should be done. A consulting pediatrician recommended surgical treatment. The obstetrician apparently counseled the family that the child would be profoundly retarded and was likely to have congenital heart disease requiring multiple operations and thus had poor chances for survival.[1] This assessment was inaccurate and contradicted the opinion that had been obtained on consultation. Baby Doe's family chose not to surgically correct the esophageal atresia and accepted the obstetrician's nonsurgical treatment.

The Indiana hospital where Baby Doe was born sought to protect itself in the conflict and requested a court judgment. The county court judge, seeing no clear medical consensus, allowed the family freedom for its own option. The county juvenile court judge found the parents to be loving and doing their best to act in the interest of the child and found no cause for further intervention. On appeal the Supreme Court of Indiana agreed. Baby Doe died before a US Supreme Court appeal could be heard.

At the end of April 1982 a memorandum was sent by President Reagan to the Attorney General and the Secretary of the Department of Health and Human Services (DHHS) specifically noting the Baby Doe case and citing federal law that prohibits discrimination against the handicapped. In May 1982 notice was sent by the Secretary of DHHS to health care providers stating, "it is unlawful for hospitals receiving federal assistance to withhold from handicapped infants nutritional sustenance or medical or surgical treatment if required to treat a life-threatening condition."[2] Failure to comply could lead to "possible termination of federal assistance."[2] Almost a year later in March 1983 the DHHS issued an "interim final rule" and, with only 15 days' notice, required all hospitals receiving federal financial aid to conspicuously display in each obstetric, maternity, pediatric and intensive care nursery unit a notice stating that "discriminatory failure to feed and care for handicapped infants . . . is prohibited by federal law. Persons having knowledge of such handicapped infants being discriminately denied food or customary medical care"[3] were advised to contact the "Handicapped Infant Hotline" and anonymity was given to callers (see Figure 1). Authorization to DHHS was given for investigation and power to initiate "legal action as may be necessary to save the life of a handicapped child." Officials were given access to the target hospital's facilities and records even at times outside normal business hours.

Under the leadership of the American Academy of Pediatrics (AAP), an injunction against this rule was sought and obtained. Federal Judge Gessell found no rational or factual basis for the rule and noted procedural inadequacies. The signs came down.

On July 5, 1983, DHHS presented a "proposed rule."[3] As before, the evidence supporting the need for this rule was based on the concern that handicapped children were being denied appropriate care because of their handicap. Few differences existed between this rule and the previous regulation except that the signs were to be smaller and to be located only at nursing stations. The "proposed rule" stated that "section 504 does not compel medical personnel to attempt to perform impossible or futile acts or therapies; yet the basic provision for nourishment, fluids and routine nursery care is a fundamental matter of human dignity and not an option for medical judgment." According to the "proposed rule" preamble, the purpose of the sign posting was "to acquire timely information concerning violations of section 504 . . . and to save the life of the infant." State agencies were to investigate and report, with DHHS carrying out the monitoring and enforcement activities. The American Medical Association led a legal challenge of the "proposed rule" and on May 23, 1984, Judge Charles L. Brieant of the US District Court of Southern New York declared the "proposed rule" unlawful and invalid. Section 504 of the 1973 Rehabilitation Act denying discrimination based on handicap was ruled not applicable.

(Lang GC: 'Baby Doe'—A medical ethical issue [Commentary]. West J Med 1985 Jun; 142:837-841)

Adapted from a presentation to the Wyoming State Medical Society Winter Meeting, Sheridan, January 21, 1984.

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The judge noted that in 2½ years of controversy, no section 504 violations had been established by the DHHS.

The House of Representatives in February 1984 passed legislation, HR 1904, establishing treatment requirements for handicapped newborns. The Senate passed its version, S 1003, on July 26, 1984, with compromise language developed through negotiations between medical, disability and "right-to-life" groups. The legislation was adopted in September 1984 after agreement by a Senate-House Conference Committee and thus is law.

This law as summarized by the AAP's "Government Activities Report" of September 1984 would

- Define a new category of medical neglect, namely, "withholding of medically indicated treatment." That offense would arise where there is found to be a

failure to respond to the infant's life-threatening conditions by providing treatment (including appropriate nutrition, hydration and medication) which, in the treating physician's or physicians' reasonable medical judgment, will be likeliest to be effective in ameliorating or correcting all such conditions, except that the term does not include the failure to provide treatment (other than appropriate nutrition, hydration or medication) to an infant when, in the treating physician's or physicians' reasonable medical judgment, (A) the infant is chronically and irreversibly comatose; (B) the provision of such treatment would (i) merely prolong dying, (ii) not be effective in ameliorating or correcting all of the infant's life-threatening conditions or (iii) otherwise be futile in terms of the survival of the infant; or (C) the provision of such treatment would be virtually futile in terms of the survival of the infant, and the treatment itself under such circumstances would be inhumane.

- Mandate that state child protective service systems have procedures in place to respond to reports of the withholding of medically indicated treatment.
- Authorize the DHHS to develop regulations.
- Authorize the DHHS to develop model guidelines for hospital committees for reviewing relevant cases, educating families and hospital personnel and offering counsel.

The federal regulations based on the new law have been proposed and are currently in the review and comment process.

The DHHS's Position

The DHHS "Baby Doe" regulations attack documented attitudes and actions of prejudiced medical care of handicapped infants.[3] Other Down's syndrome infants with various gastrointestinal tract atresias are reported to have been treated similarly to Baby Doe.[4] Articles in the pediatric literature report pediatrician and pediatric surgeon attitudes that may be prejudicial by handicap in medical care decisions for infants with Down's syndrome.[4,5]

The American Academy of Pediatrics's Position

The AAP is dedicated to serving children. The basic objectives of the "proposed rule" were not questioned by the AAP. There was open concern that Baby Doe's obstetric physician made a mistake, that poor advice was given to the family and that such an event should be avoided. Nevertheless, the AAP is strongly against federal intervention through regulation, threat, distrust and suspicion. "Hotline harm," federal investigation squads responding to anonymous calls and inserting themselves in already difficult situations with the forces of a procedural puzzle and legal threats, seems to be the antithesis of the goals of pediatric medical care. The Academy feels that harm could be and was done by these squads.[6] James E. Strain, MD, then President of the American Academy of Pediatrics, wrote in his "Letter to Academy Fellows" on July 29, 1983, that the Academy was concerned that the rules are contrary to the President's own Commission for the Study of Ethical Problems in Medicine's recommendations for care in such circumstances and also in conflict with the AAP's Committee on Bioethics statement on the "Treatment of Critically Ill Newborns."[7] The "proposed rule" was

NOTICE

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Office for Civil Rights

DISCRIMINATORY FAILURE TO FEED AND CARE FOR HANDICAPPED INFANTS IN THIS FACILITY IS PROHIBITED BY FEDERAL LAW. SECTION 504 OF THE REHABILITATION ACT OF 1973 STATES THAT

"NO OTHERWISE QUALIFIED HANDICAPPED INDIVIDUAL SHALL, SOLELY BY REASON OF HANDICAP, BE EXCLUDED FROM PARTICIPATION IN, BE DENIED THE BENEFITS OF, OR BE SUBJECTED TO DISCRIMINATION UNDER ANY PROGRAM OR ACTIVITY RECEIVING FEDERAL FINANCIAL ASSISTANCE."

Any person having knowledge that a handicapped infant is being discriminatorily denied food or customary medical care should immediately contact:

Handicapped Infant Hotline
U.S. Department of Health and Human Services
Washington, D.C. 20201
Phone 800-368-1019 (Available 24 hours a day) - TTY Capability

In Washington, D.C. call 863-0100

OR

Your State Child Protective Agency

Federal Law prohibits retaliation or intimidation against any person who provides information about possible violations of the Rehabilitation Act of 1973.

Identity of callers will be held confidential.

Failure to feed and care for infants may also violate the criminal and civil laws of your state.

Figure 1.—The notice from the March 1983 "Interim Final Rule."

taken as an insult and not a positive remedy for the basic problem of human rights for handicapped infants.

The Academy, though, does recognize that mistakes can be made by physicians and families and that government and society have an interest of advocacy for infants and children. Recognizing these problems and the lack of medical and legal consensus, the physician is nevertheless directed by his or her duty to the child, the patient. We all know that errors can be and are made, recognizing that our pediatric patients cannot speak for themselves; that physicians may lack adequate diagnostic, prognostic and treatment facts; that pressures can be exerted by society and family, and that personal prejudices exist. Accountability for these difficult decisions is sought. To help resolve this problem, the AAP recommends counsel and review by a local bioethics committee. The Academy strongly rejected the "proposed rule" as government's blundering intervention into a very delicate professional ethical area that, needing focus, can be constructively addressed by local bioethical committees.

Special Points

There are some special points about this whole affair that I would like to mention.[8] First of all, these rules and regulations enter into our local private and professional lives in a very reckless fashion from a Republican administration dedicated to deregulation and to decentralization. The President himself has established a Bioethics Commission whose recommendations released in the spring of 1983 concur with the position of the AAP and are in conflict with the DHHS "proposed rule." It seems remarkable that the "proposed rule" separates medical decisions from decisions that are considered by government to be for the well-being of children. It is a pity that parents are almost totally ignored in the Baby Doe issue and that the implementation of the rules seems to cruelly insult parents at a most delicate time in their family lives. The suspicious and adversarial nature of the "proposed rule" interjected into our nurseries and wards is uncomfortably unsuited for our western medical tradition in this free democratic society. Infanticide, euthanasia and child abuse are the undercurrent accusations. "Not all judgments made by health care providers . . . are medical judgments."[3] Thus the coarse, callous nature and harsh manner of implementation coupled with so many contradictions created a unique challenge for physicians.

What Are the Issues of Consideration in Treatment Decisions?

Is life in itself absolute and the ultimate value? If *sanctity* of life[9] is our goal, then we face the corollary that death represents failure and is the antithesis of treatment. With life being the ultimate treatment goal, then death is the ultimate failure. The arguments of the current "right to life" advocates are flavored with the sanctity principle and declare that any alternatives to "the sanctity of life" are immoral. With this concept we would ventilate brain-dead corpses.[1]

It was Pope Pius XII[10] who promulgated the distinction between *ordinary* and *extraordinary* treatment in helping to make treatment decisions. The definition of ordinary and extraordinary is in a fluctuating state reflecting changes in technical ability, medical knowledge and standards. Each of us has our own idea of what ordinary and extraordinary mean. Of greatest danger is that ordinary care can be defined as simple, inexpensive, customary and convenient.[1] Certainly, many times these factors are not in the best interest of our patients.

Treatment decision making can be made using concepts based on the *quality* of life. Baby Doe was denied surgical treatment because of the "impaired qualities" of Down's syndrome. The obstetrician felt that the handicap denied adequate quality to Baby Doe's life and surgical treatment was limited accordingly. Different cultures deal with this quality issue more directly; infanticide is a frequent standard in many cultures. A Peruvian pediatrician training with me marveled at the adult Down's syndrome patients in the United States. He had never before seen an adult with Down's syndrome. He stated, "In Peru they're all thrown from a cliff." Suicide and euthanasia generate their strongest support from those who cite declining quality as the primary factor in such decisions. Quality is not universally defined or standardized. Quality changes. "Who speaks for the quality of life yet to be lived?"[11] A ventilated corpse has quality to those who believe in the sanctity of life and thus to them strongly mandates for such medical treatment. At the other extreme, temporary situational depression can lead to a seemingly logical suicide, yet we all recognize the transient nature of such situations. We have a strong goal to prevent and treat and to avoid sanctioning and condemning such decisions. Treatment decisions based on quality are quite vulnerable.

When life is considered as sacred but not in itself ultimate or absolute, a recognition of life's *limits* is implied. This concept of limits is common in our western civilization. With inherent limitations in life, it is implied that the obligation to treat is limited. The direction to treatment becomes based on whether or not benefit exists.[1]

The balance of individual *benefit* and *burden* of treatment is a consideration familiar today as "cost-effectiveness" or "risks versus benefits." Treatment or care whose burden is greater than benefits clearly is the opposite of our medical thesis, "first do no harm." Certainly, those who balance the benefits and burdens would abhor ventilated brain-dead corpses as a medical goal. Father John Paris, in a 1983 speech to a meeting of AAP chapter chairmen, addressed this issue directly and emphasized that "a physician's role is not necessarily to cure but always to care, to provide company, comfort and compassion with our patient's interest being our physician goals."[1]

Who Speaks for the Patient?

What happens when a patient is unable to speak for himself or herself? What happens to the newborn infant, the child, the geriatric patient with Alzheimer's disease? Who will speak for the next Baby Doe?

During the last election our politicians raised their hands and said, "I will speak." As it was noted in the *Wall Street Journal,* "The President gets it into his head that the 'right to life' people have identified a serious threat to handicapped newborns. Why not throw them the bone of a full-blown DHHS rule?" ("Infants," April 18, 1983, p 24). Our government of special-interest-based politicians feels the pressure to support each special group's special desires. With changing political wind, one day our treatment might be directed, as in the Baby Doe case, to "right to life" sanctity of

life concepts. Yet, with another day, another wind and another President, perhaps decisions on life would be made according to quality. What if Hitler were our President?

If we allow the laws and courts to make medical treatment decisions for our patients who are unable to speak for themselves, confusion will reign. Father Paris likened that disaster to a situation of "cannonballs free on a rolling ship." We want the lawyers and courts out of our hospitals, and we as physicians need to accept a role that urges them out. And when they threaten us? Yes, well-meaning physicians have been hauled into court and charged as murderers. We need to show them the *big stick* we carry: our training, our medical practice, our ethics and our tradition.

The bureaucrats and their rules and regulations are just as important as our politicians and lawyers when standing between the doctor and patient. Certainly it is appropriate for society to assure human rights and to assure the well-being of its dependent and incompetent members. But the harshness, the lack of public control and the moats and mazes that protect our bureaucrats seem to have no meaningful role in treatment decisions.

Shall we let technology speak for us? It is conceivable that in the future a computer printout would state, *"Intubate patient, insert central venous pressure line, insert central arterial line, insert probes, insert monitors,"* and doctors would obey and say, *"I will proceed with care. Show me the way."* Will we eventually give up to the machines, to computer printouts? If technology is available and if drugs are available, then must they be used? No—they must be used only if they benefit our patients.

Shall the theologians or our religious leaders decide? Which religion are you? Which religion is your patient? Which religion is right?

Politics, bureaucrats, courts, machines and churches are really a part of society. Let's let society decide how to treat. But there are local and regional differences in our social values. There is no standard. Why do we spend hundreds of thousands of dollars on high-risk premature infants when there are starving children in Africa? Where are our society's pressures and priorities? Where are our society's special interests and prejudices? Do our welfare babies get the same treatment as a Kennedy's? Who decides who is going to spend how much on whom? Society's money is limited and the care thus will be prioritized. You have seen that. Do you want society's bureaucrats directing dollars and therefore deciding how to treat our patients? No. Who speaks for society anyway? We must understand the risk of having general societal pressures actively involved in day-to-day medical treatment decision making.

Some would say the physician should decide. The physician has the unique role of being primarily and solely responsible to the patient's best interests. The physician has a separate responsibility to medical ethical traditions and standards. Yet, physicians make mistakes and these mistakes can be both with and without malice or knowledge. There can be errors in diagnosis. Prognosis can be notoriously inaccurate, and an accurate assessment of priorities sometimes is seemingly impossible. Physicians are not standardized. There is no national physician norm. There is inadequate control. The physician has great fear. There are threats of reprisal for malpractice and accusations of murder if a physician is perceived to miscue. Physicians need both guidance and protection.

Let us turn to the family, for certainly the family must best speak for the child; he or she is their child. They bear the burden of raising the child. They carry the financial responsibility, the pleasures of success and the pains of failure. A family certainly should decide, some would say. But families can make poor decisions both because of inadequate education or understanding or because of personal or religious prejudice. Families can be pathological and abusive. Families can be self-serving, seeking to perpetuate their own structure, and not necessarily act in the best interest of their children. Nevertheless, courts recognize that families do have a judgment role. This role exists especially when evaluating risks versus benefits in elective procedures.[12] The ultimate control for a child's welfare has been usurped from the family by the courts. The family alone cannot make a decision but nevertheless cries out, "It is notable how often solutions are proposed which involve other people doing the actual day-to-day caring."[13]

Decision by committee—that seems like a logical solution, and the President's Commission and the American Academy of Pediatrics have recommended it. There are committees for everything; why not another committee? Committees would have the advantage of diffusing responsibility, of being objective and of evaluating from different perspectives. Committees are society's workhorses when all other methods seem to have failed. But we all know that committees take time, committees are boring and committees can make mistakes. Our Surgeon General is worried that committees may not meet the needs of the law in enforcing and protecting the civil rights of handicapped infants (C. E. Koop, "Should Uncle Sam Protect Handicapped Babies?" *US News and World Report*, January 16, 1984, pp 63-64). Who controls the committees? To whom is the committee responsible? How are the committees organized and run and who reviews the committees' actions? The answers are indistinct and not adequate. And even if there were committees, Dr Koop, the Surgeon General, still wants the "signs on the wall."

How does this affect physicians in my own state of Wyoming, for example? I am struck by the fact that much of the Baby Doe issue was precipitated by a small town obstetrician making a serious judgment error. He rejected the weight of consultation and he acted prejudicially and out of ignorance. He abused the power of the delicate doctor-patient relationship. We would all seek to avoid such mistakes. I think that we should all pay very close attention to the Baby Doe issue because it is at the forefront of medical ethical thought and change. We all have patients who cannot speak for themselves.

I predict that in time each of our communities will have a bioethics committee. You need one more committee in your medical staff. Change is coming.

I predict that if we do not get the signs out of the nurseries, there will be signs in intensive care units, signs in emergency rooms and signs in operating suites. These signs will direct anonymous callers to insert "big brother" between you and your patients' lives. These intrusions of our privacy will come and it is our challenge to face them head on and seek to avoid them now.

Conclusion

As medicine changes, we need to change. With new influences and new scrutiny, with new knowledge and technology and with changing ethics and sensitivities, we must remember that our first goal is to serve our patients. Jim Strain, a Denver-based pediatrician and past president of the AAP, says, "Not all babies can be born healthy or whole, but individuals directly involved with infant care can work together to treat, comfort and ease a seriously ill child."[14]

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Medical Practice Question

EDITOR'S NOTE: *From time to time medical practice questions from organizations with a legitimate interest in the information are referred to the Scientific Board by the Quality Care Review Commission of the California Medical Association. The opinions offered are based on training, experience and literature reviewed by specialists. These opinions are, however, informational only and should not be interpreted as directives, instructions or policy statements.*

Multiple Injections of Sclerosant Solution

QUESTION:

Is it accepted medical practice to use multiple injections of a proliferant, also known as sclerosant mixed pyrogen-free water, in the management of neck, back and lower extremity pain?

OPINION:

In the opinion of the Scientific Advisory Panels on Neurology, Neurosurgery and Orthopedics, the use of multiple injections of a sclerosant solution, consisting of 25% phenol, 25% dextrose and 25% glycerin mixed with pyrogen-free water to 100%, in the management of neck, back and lower extremity pain is considered unacceptable medical practice. The use of sclerosant agents for such treatment is based upon the assumption that the pain is related to a derangement of the ligamentous structures. The hypothesis further assumes that the pathogenesis can be clearly defined and differentiated from other causes, that the compromised ligaments can be identified and that the pathogenesis involves a weakening of the ligaments that can be strengthened by injecting agents which cause inflammatory changes and ultimately fibrosis. This hypothesis has not been proved. In fact, there have been no double-blind studies that have documented the safety and effectiveness of this technique.

Though the concept of this treatment has been around for a number of years, it has not gained acceptance. Until scientific evidence provides otherwise, sclerosant therapy for neck, back and lower extremity pain cannot be accepted as standard practice—indeed, its use may be potentially harmful.

Topics in
Primary Care Medicine

Outpatient Treatment of Chronic Obstructive Pulmonary Disease—A Practitioner's Guide

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"Topics in Primary Care Medicine" presents articles on common diagnostic or therapeutic problems encountered in primary care practice. Physicians interested in contributing to the series are encouraged to contact the series' editors.

BERNARD LO, MD
STEPHEN J. McPHEE, MD
Series' Editors

Chronic obstructive pulmonary disease (COPD), a collective term including emphysema, chronic bronchitis and adult nonallergic asthma, affects millions of persons in this country and is the 11th most common cause of death. Major advances have been made in the pharmacologic management of these patients over the past ten years. To provide a simple but fairly comprehensive guide for physicians who treat this disease in an outpatient setting, we have used a new method of displaying patient care decisions called a criteria map. This map (Figure 1) defines the major problems of these patients and offers specific suggestions, tailored to individual patient characteristics, regarding testing and therapy. The map was designed by a group of community-based primary care physicians and university-based pulmonologists (M.S.S., H.A.B.) to reflect both scientifically based "ideal" treatment and the practical demands of primary care practice. Where applicable, options are offered for tailoring a treatment plan to specific needs of a patient. Certain treatments, such as intermittent positive pressure breathing, have been omitted because they are controversial or of unproved value, though they may still be of use in carefully selected patients. The map, or indeed any guide to treatment, assumes that a patient's disorder has been correctly identified. The criteria for diagnosing COPD have been well described.

The criteria map deals with four major areas of outpatient care in cases of COPD: review and treatment of symptoms, review of medications and their side effects, laboratory monitoring and prophylaxis and education. Although not necessarily included in every office visit, these are the basic components of outpatient care.

Using a Criteria Map

This criteria map is designed to simulate a normal comprehensive office visit of a patient previously diagnosed as having COPD. Each major section of the map (A through D) should be entered and completed for each patient. Within each section of the map are questions about possible symptoms, side effects, signs or laboratory test results. In each case, the response to the explicit or implied question leads to either an additional question or a recommended action (or a group of optional actions).

Review and Treatment of COPD Symptoms (Section A)

The map begins with an assessment of the major symptoms of COPD: dyspnea, wheezing, chest tightness and cough. If these symptoms have developed or worsened since the previous visit, the physician should exclude infection and heart failure before attributing the symptoms strictly to worsening of the airway disease.

Symptoms of infection such as fever, coryza or discoloration of sputum may be caused by pneumonia (bacterial or not), tracheobronchitis or a viral syndrome. Examination of the patient is mandatory. Fever, especially in the presence of new localized rales, suggests parenchymal infection. Depending on the severity of the apparent infection, the physician may choose to evaluate the sputum, obtain a chest x-ray

(Stulbarg MS, Gerbert B, Kemeny ME, et al: Outpatient treatment of chronic obstructive pulmonary disease—A practitioner's guide [Topics in Primary Care Medicine]. West J Med 1985 Jun; 142:842-846)

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ABBREVIATIONS USED IN TEXT

COPD = chronic obstructive pulmonary disease
FEV_1 = forced expiratory volume in one second

film or treat empirically with a broad-spectrum antibiotic, such as tetracycline, ampicillin or trimethoprim/sulfamethoxazole. If rales and fever are absent, the physician may choose to observe the patient or to empirically give a course of antibiotics for reducing the typically mixed bacterial flora found in sputum cultures of patients with exacerbations of COPD. If in addition to worsening dyspnea a patient reports edema, orthopnea or paroxysmal nocturnal dyspnea, congestive heart failure should be considered. The findings of a left-sided third heart sound gallop and new rales would support this diagnosis but, even in the absence of these physical findings, a chest radiograph may show the typical findings of left ventricular failure: cardiomegaly, vascular redistribution and increased interstitial markings (Kerley B lines).

In the absence of evidence of heart failure or infection to explain the worsening of a patient's symptoms, certain tests may be helpful. The map presents the decision to do testing as optional, for it depends on many difficult-to-define factors such as a physician's familiarity with the patient, the patient's response during previous similar episodes and a judgment as to the reliability of the history.

Pulmonary function studies, such as the forced expiratory volume in one second (FEV_1), may be particularly helpful if they show significant worsening—that is, 20% or more—as a change of this magnitude usually requires more intensive therapy. Arterial blood gas values may indicate hypoxemia severe enough to require further evaluation and, if hypoxemia persists, oxygen supplementation. Without a clear-cut historical, physical or laboratory explanation for a patient's deterioration, a chest radiograph may be obtained to uncover otherwise silent problems such as pneumonia, heart failure or lung cancer.

In doing a diagnostic workup of a patient whose symptoms have worsened, the next step is to determine if the medication regimen is optimal. The two major categories of drugs used for treating COPD are bronchodilators and corticosteroids. Cromolyn sodium is rarely effective in the treatment of COPD and has been omitted from the map. The bronchodilators include theophylline preparations and oral and inhaled sympathomimetics. The physician panel generally preferred the new long-acting theophylline preparations. The precise definition of "maximal" dosages of these drugs is difficult and may be controversial, but the following guidelines were selected: (1) a "maximal" dosage of a theophylline preparation has been reached when peak blood concentrations of the drug are between 15 and 20 mg per liter or when intolerable side effects have occurred, such as nausea, vomiting, diarrhea, tremors or insomnia; (2) blood concentrations of sympathomimetic drugs are not yet available, so the upper dose range is defined by the presence of limiting side effects—that is, tremors or palpitations—or the use of the maximum dosage recommended by the manufacturer (metaproterenol sulfate, 20 mg four times a day; terbutaline sulfate, 5 mg three times a day; albuterol sulfate, 4 mg three times a day), and (3) the inhaled sympathomimetic dosage is considered "maximal" if a patient uses 12 puffs per day in divided dosages (metaproterenol, 600 μg per puff; albuterol, 90 μg per puff; terbutaline, 200 μg per puff, or isoetharine, 300 μg per puff), although this level may still be inadequate for some patients. If symptoms have not resolved satisfactorily after the bronchodilator regimen has been increased to a maximum level, then the physician should prescribe a brief course of oral corticosteroids (usual starting dose, 0.5 to 1.0 mg per kg of body weight per day of prednisone or equivalent), order additional laboratory studies, obtain a consultation or recommend admission to hospital.

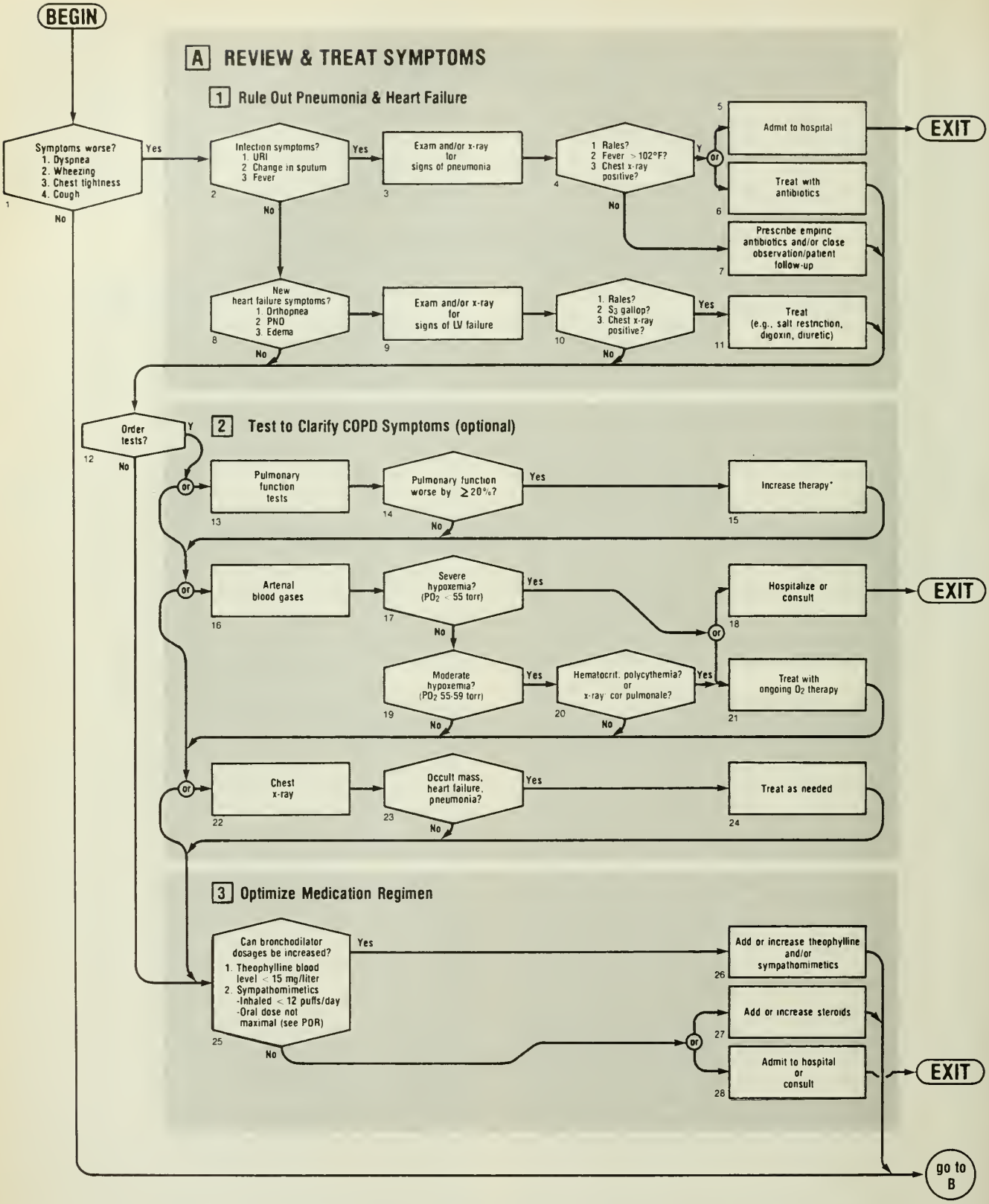
Review Medications (Section B)

A specific review of the medication regimen is vital to evaluate compliance, monitor side effects and assure that steroids have been reduced to a minimal level. In the presence of major bronchodilator side effects such as seizures or serious cardiac arrhythmias, the physician must discontinue the medications immediately and admit the patient to hospital. With minor side effects—gastrointestinal or nervous system disturbances such as tremor or minor cardiac arrhythmias—the physician may choose to lower the drug dosage empirically, measure the theophylline blood concentration to determine if it is increased or pursue an alternate plan, such as reassuring and advising the patient while observing for persistence of the side effects. If the theophylline concentration is measured, a value greater than 20 mg per liter indicates that the dosage must be lowered. Even if the concentration is in the "therapeutic" range, between 10 and 20 mg per liter, the dosage may be lowered in the hope of eliminating the side effects. If the value is less than 10 mg per liter, the physician should look for an alternate explanation of the side effects, although occasionally patients will be intolerant of even very low dosages of theophylline.

Side effects from long-term oral corticosteroid therapy are well known. No dose is considered totally safe, and in all cases the physician should taper the corticosteroid to the lowest dose that allows a patient to function at an "acceptable" level. Major side effects from corticosteroids such as infections, gastrointestinal bleeding, severe hypertension or severe psychiatric disorders indicate the need for immediate admission to hospital. Less serious side effects such as edema, acne, weight gain, cataracts, hypertension, hyperglycemia and many others can be minimized (but not always avoided) by lowering the dosage of corticosteroids, adopting an every-other-day regimen or substituting inhalation of beclomethasone dipropionate, to a maximum of 20 to 24 puffs (50 μg per puff) per day in divided doses. Inhaled corticosteroids are nearly free of the side effects that accompany systemic therapy, though oral candidiasis and hoarseness may occur. Inhaled corticosteroids are therefore a more reasonable choice for ongoing use earlier in the management of COPD than are orally given corticosteroids, especially in patients who do not tolerate the use of oral bronchodilators well. Patients with severe airflow obstruction or with acute exacerbations of COPD may have difficulty tolerating inhaled beclomethasone, so its use is often begun after a brief course of oral corticosteroids.

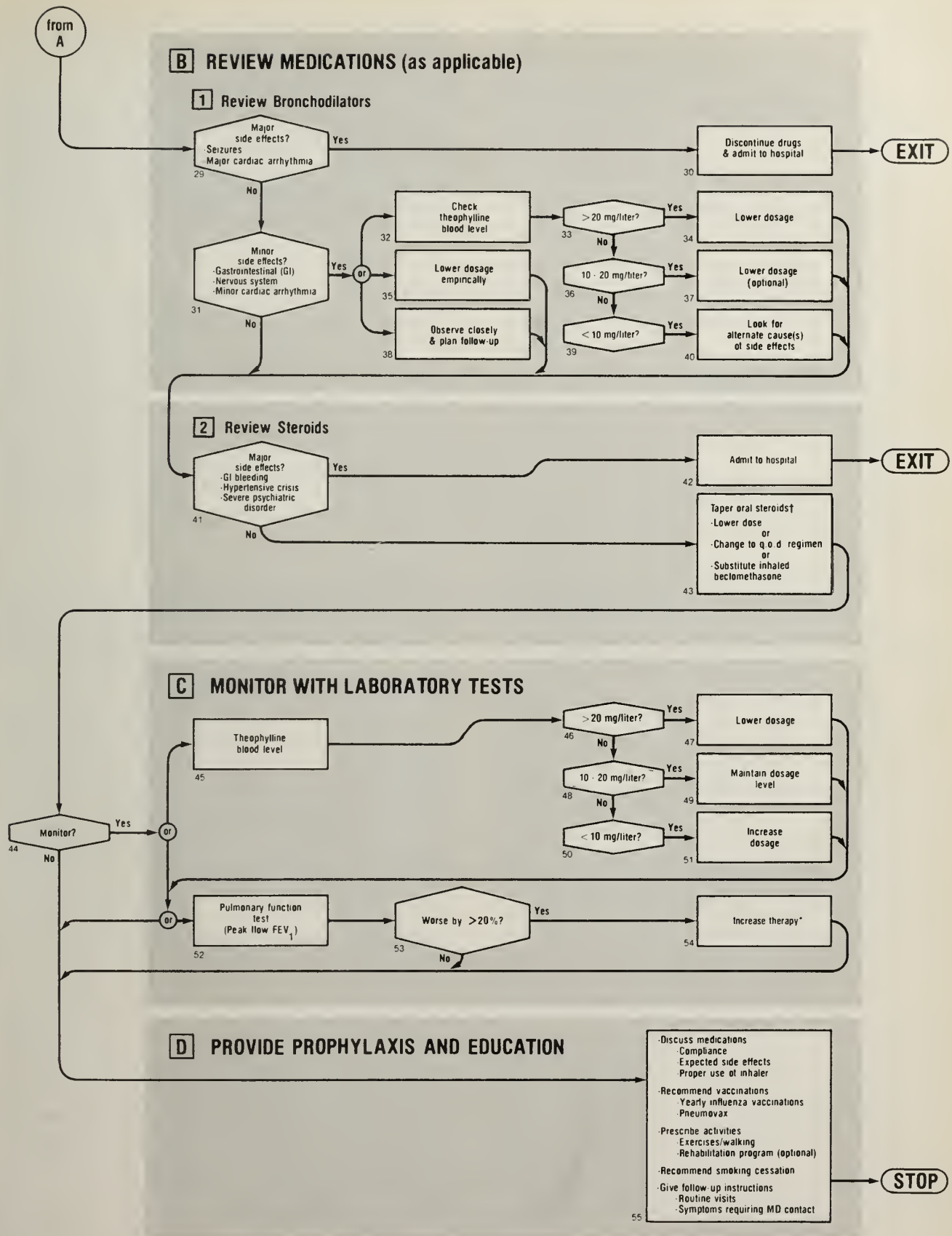
Laboratory Monitoring (Section C)

Even in the absence of uncontrolled symptoms or drug side effects, two laboratory tests may be of assistance in moni-



FEV_1 = forced expiratory volume in one second. LV = left ventricular; PDR = *Physician's Desk Reference*; PND = paroxysmal nocturnal dyspnea; q.o.d. = every other day; URI = upper respiratory [tract] infection

Figure 1.—A "criteria map" for chronic obstructive pulmonary disease (COPD). The map deals with four major areas of outpatient care in cases of COPD: **A**, Review and treatment of symptoms; **B**, Review of medications and their side effects; **C**, Laboratory monitoring; **D**, Prophylaxis and education. The criteria map has a BEGIN point, EXIT points when a patient enters the hospital or is sent to a chest physician for consultation and a STOP when the four sections of the maps have been traversed. Hexagonal shapes represent possible signs and symptoms of COPD patients; rectangles indicate subsequent physician actions. Arrows direct one from signs or symptoms to physician actions through each section and from one section to the subsequent section. When several alternative actions are acceptable, **or** signs appear in the map.



*"Increase therapy": Add or increase theophylline, oral or inhaled sympathomimetics or inhaled corticosteroids. If these are all at maximal levels (see box #25), oral corticosteroids may be added to the regimen.

†"Taper oral steroids": Physicians should attempt to taper doses of oral corticosteroids at all times.

toring drug therapy for patients with COPD: measurement of theophylline blood concentrations and pulmonary function studies. The map presents treatment options in this section based on the results of these tests independent of changes in symptoms. In the absence of side effects, a blood theophylline concentration of less than 10 mg per liter indicates that an increased dose may result in greater clinical benefit. With a value between 10 and 20 mg per liter, the dosage should normally be maintained. A value greater than 20 mg per liter would call for immediate downward dose adjustment.

Pulmonary function studies, such as spirometry, can also be used for periodic monitoring of a patient's condition, both to better understand the course of the person's disease and to identify deterioration of which the patient may be unaware. Simple and inexpensive spirometers are readily available for outpatient measurements. The panel decided that 20% or greater deterioration in pulmonary function, such as in decreased FEV_1, requires either some change in a patient's therapeutic regimen or the decision to follow the patient more closely to be sure the deterioration is sustained before augmenting the therapy.

Prophylaxis and Patient Education (Section D)

Education and prophylaxis are critical components of the outpatient care of patients with COPD. We believe that better patient understanding of the nature of the disease and the benefits and side effects of medications results in better cooperation with the therapeutic regimen. Printed educational materials may augment physician instruction. At every visit, the physician should specifically review the drug regimen regarding compliance and side effects. Because misuse of metered-dose inhalers is common and may be a cause for apparent "failure" of inhaled bronchodilator or corticosteroid therapy, repeated instruction in the use of the inhaler is important (Table 1). Such instruction should also emphasize the possible harm of inhaler overuse. Newly described reservoir or spacer devices (Aerochamber by Monaghan Medical Corporation or InspirEase by Key Pharmaceuticals) may be useful for some patients who have difficulty with the proper use of inhalers or in whom local side effects develop from them. Follow-up plans should include not only regular appointments but also instructions as to when to call the physician because of complications or exacerbations.

TABLE 1.—*Instructions for Correct Use of Metered-Dose Inhalers*

Hold inhaler with canister inverted and shake well
Place mouthpiece between teeth or just outside the open mouth (keep tongue and teeth from blocking the opening)
Exhale to the end of a normal breath
Activacte the inhaler *while* slowly breathing in to full inspiration
Hold the breath for 5 to 10 seconds and exhale slowly
Wait 1 to 20 minutes before repeating

Discussion of activity and exercise is important, for patients may inappropriately restrict their activity because of dyspnea. Specific recommendations should be given regarding home activities (including sexual intercourse) and choice of exercise. Referral to rehabilitation programs is appropriate for many patients. An influenza vaccination should be offered annually and pneumococcal vaccination (Pneumovax) should be given once. The patient's smoking history should be reviewed periodically even if the patient claims to have quit. If a patient continues to smoke despite strong and unambiguous physician advice, specific steps should be taken such as referral to smoking-abatement clinics or the use of nicotine resin chewing gum (Nicorette) should be recommended.

Conclusion

The care of a patient with COPD is demanding for both the patient and the physician. Careful attention to the details of care discussed here can make a dramatic difference in the quality of the patients' lives, may decrease hospital stays and days of disability and may even have an impact on longevity.

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Special Article

Inherent Contrast in Magnetic Resonance Imaging and the Potential for Contrast Enhancement

The 1984 L. Henry Garland Lecture

Presented at the Annual Meeting of the California Radiological Society, Monterey, California, May 5, 1984.

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Magnetic resonance (MR) imaging is emerging as a powerful new diagnostic tool valued for its apparent lack of adverse effects. The excellent inherent contrast between biologic tissues and fluids afforded by MR imaging is one of the foremost characteristics of this technique and depends on physicochemical properties such as hydrogen density and T1 and T2 relaxation rates, on magnetic field strength and on operator-chosen factors for acquiring the MR imaging signal. Pharmaceutical contrast-enhancing agents shorten the MR imaging process and improve sensitivity and diagnostic accuracy.

(Brasch RC: Inherent contrast in magnetic resonance imaging and the potential for contrast enhancement—The 1984 L. Henry Garland Lecture. West J Med 1985 Jun; 142:847-853)

As an introduction I will recount a conversation I had recently with an old friend, a surgeon, whom I had not seen for several years. When he asked what type of research I was involved in, I explained that our group was studying magnetic resonance (MR) imaging, formerly known as nuclear magnetic resonance imaging, and, in particular, we were attempting to develop new pharmaceutical contrast agents for this technique. Being a well-informed physician, my friend explained that he knew a little about MR imaging and that he understood that it had excellent inherent contrast. He asked, "Why do you need contrast agents at all for MR imaging?" He also asked, "How do these new contrast agents work?" Had I the time at the occasion of our meeting, I would have offered the following as answers to his questions.

Determinants of Contrast on Magnetic Resonance Images

Hydrogen MR images of the human body are now being obtained by adding small amounts of energy to the body's protons in the form of radiofrequency pulses, or radiowaves, after the patient has been placed within a strong external magnetic field. Following the radiofrequency pulse, the magnetic axes of the protons, which have a natural tendency to oscillate or "resonate," return to equilibrium by emitting radiofrequency energy. This energy is detected by the MR device and converted into a two-dimensional tomographic image in any one of three orthogonal planes (transaxial, coronal or sagittal). The process of nuclei returning to equilibrium is called "relaxation" and the time constants for relaxation for a tissue vary depending on the chemical environment of the protons within the tissue.[1-3] For example, hydrogen protons in bone are in a rigid matrix and tend to relax slowly, whereas protons in bone marrow, a relatively fatty tissue, relax quickly. The differences in hydrogen concentration and relaxation times of hydrogen within different tissues are primary determinants of contrast on MR images. There are, in fact, two relaxation constants for each tissue called the T1 and T2 values. For a more detailed discussion of the principles of hydrogen MR imaging, the reader is referred to one of several excellent reviews.[1,4-6]*

There are factors important to MR imaging contrast in addition to hydrogen concentration, T1 and T2. Certain of these factors depend on the MR imaging device used; others are dependent on physical conditions of the tissue such as viscosity and temperature. Contrast between tissues will vary among imaging systems operating at different magnetic field strengths. The commercially available imaging systems offer

*See also the two-part article by W. R. Hendee and C. J. Morgan in the October and November 1984 issues of *The Western Journal of Medicine*, "Magnetic Resonance Imaging: Pt I—Physical Principles; Pt II—Clinical Applications," Vol 141:491-500; 638-648.

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Supported in part by grants from the National Institute of Arthritis, Diabetes, Digestive and Kidney Diseases (AM 31937) and from the research department of Schering AG, Berlin.

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ABBREVIATIONS USED IN TEXT

CT = computed tomography
DTPA = diethylenetriaminepentaacetic acid
LD_{50} = median lethal dose
MR = magnetic resonance
NSL = nitroxide spin labels
TE = echo delay time
TR = pulse interval

a range of magnetic field strength from 0.15 to 2.0 tesla. The optimal choice of field strength for MR imaging is a controversial subject and goes beyond the scope of this discussion; it is sufficient to note that contrast differences will tend to decrease at higher field strengths. But other variables such as signal-to-noise ratio tend to improve at higher field strengths.

Another important determinant of contrast is the sequence and spacing of radiofrequency pulses used to excite the body's protons. These pulses are applied repeatedly. The commonly available choices of pulsing sequences include inversion recovery, spin echo and saturation recovery sequences.[5,6] Each pulse sequence emphasizes different magnetic characteristics of tissues and each produces distinctively different tissue contrast and grey scales. Further, there is virtually an infinite variety of pulse intervals (TR) and echo delay (TE) times, each TR-TE combination yielding a different intensity value (shade of grey) for the same tissues. No single pulse sequence or TR-TE combination is best to emphasize contrast between all normal tissues and pathologic processes. Accordingly, an MR imaging examination will generally include multiple pulse sequences, TR-TE combinations or both in hopes of obtaining a good or best contrast scale.

Thus, numerous factors determine the observed contrast on an MR image, some factors inherent to the tissues themselves and others depending on the equipment used or operator-chosen pulse sequences. One can easily appreciate a possible disadvantage—too many choices. A radiologist could gather dozens of different images from a single patient over many hours without exhausting all possibilities. There must be a limit to the number of images obtained without a major loss in available information or diagnostic confidence. Pharmaceutical contrast agents may help to alleviate this problem by selectively increasing the intensity of pathologic processes and thereby minimizing the need for additional imaging sequences. Contrast enhancement could shorten the total time for the MR imaging examination and thus improve the cost effectiveness of the technique.

Another rationale for the use of contrast enhancement of selected tissues is to increase the contrast differences between magnetically similar tissues. Studies of animals with MR imaging and anecdotal clinical experiences indicate that contiguous normal and abnormal tissues may have identical or closely approximating relaxation values and hydrogen concentrations.[7-9] These "isomagnetic" tissues cannot be differentiated by MR imaging regardless of imaging system or operator-dependent variables. The precise incidence of isomagnetic pathologic processes is unknown but may be relatively low compared with the occurrence of "isodense" lesions on computed tomographic scans. Regardless of the incidence, pharmaceutical contrast agents could permit the differentiation of isomagnetic lesions and increase confidence that a lesion is not being missed.

Inherent Contrast on Magnetic Resonance Images

Normal Physiologic Contrast

The intensity differences—that is, the variations in grey—among many normal tissues on MR images are often striking and uniquely valuable. Many contiguous tissues that cannot be reliably separated by computed tomography, ultrasound or conventional radiography without extrinsic contrast media can be easily differentiated by MR imaging.[9] Noteworthy examples of useful inherent MR imaging contrast differences include grey and white matter of the brain (Figure 1), cortex and medulla in the kidney, compact bone and medullary spaces (Figure 2), the spinal cord and the subarachnoid space, the annulus fibrosis and nucleus pulposus in intervertebral discs (Figure 3) and even concentrated and dilute bile.[10]

Another extremely useful property of MR imaging is the sharp contrast observed between rapidly moving blood and static tissues such as blood vessel wall (Figure 4.)[11] Emitted radiofrequency signals from fast-moving blood are totally or nearly totally missed by the MR detector system so that blood appears low in intensity (black). Blood vessel walls and the heart, particularly on electrocardiographic-gated MR images, have a relatively high intensity. These properties of MR imaging, in effect, provide angiographic detail of vascular structures without contrast medium administration. Addition-

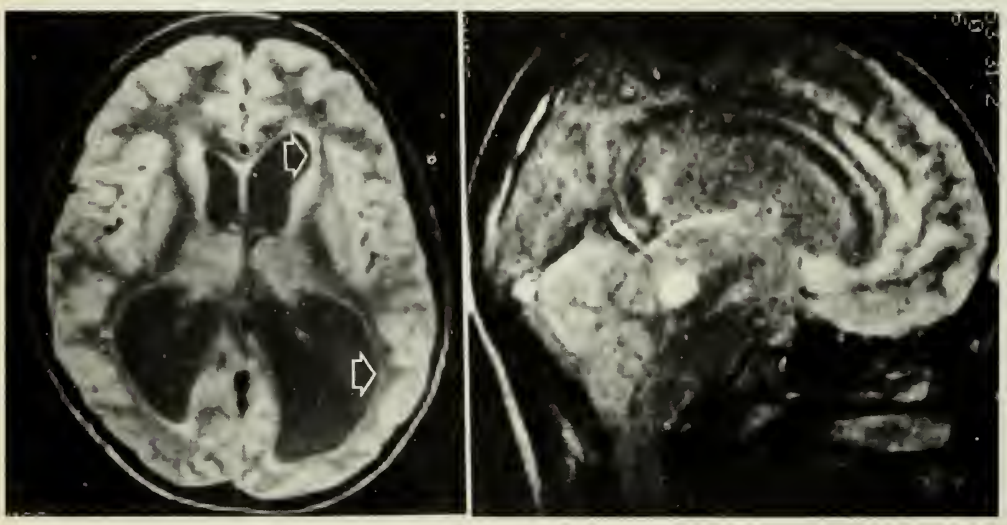

Figure 1.—Left, A transverse spin-echo magnetic resonance image of the brain without contrast enhancement shows excellent grey- and white-matter contrast differences, substantial ventricular enlargement and a rim of periventricular edema (arrows) from cerebrospinal fluid (CSF) obstruction. **Right,** A sagittal image of the same patient clearly defines a high-intensity midbrain glioma, the cause of CSF obstruction.

ally, it may be possible to quantitate the rate of blood flow within vessels using only the nonenhanced MR images.

Contrast Differentiation of Normal and Abnormal Tissues

The high sensitivity of MR imaging for a variety of pathologic processes is described in numerous articles now appearing in the radiologic and MR imaging literature.[9-12] Of note, there are at least two journals devoted exclusively to MR applications in medicine. Recognized applications of MR imaging include the detection of demyelinating processes of the central nervous system, infarction of various tissues including the brain and heart, inflammatory processes, edema

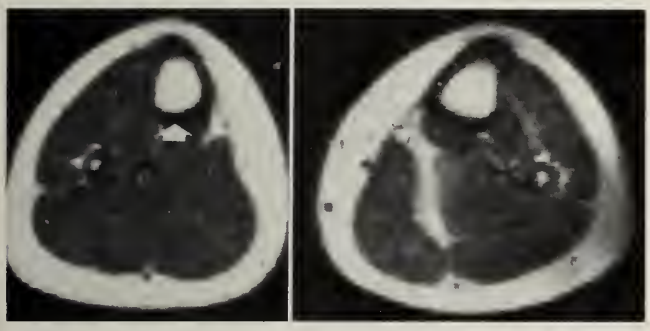

Figure 2.—A transverse spin-echo image of the lower leg in a boy with hemophilia shows high contrast between clotted blood in a hematoma and surrounding muscle. Notice the high intensity of marrow in the tibia contrasted by the low-intensity (black) cortical bone (arrow).

Figure 3.—Magnetic resonance (MR) imaging produces a sharp contrast difference between the nucleus pulposus (high intensity) and the annulus fibrosis (low intensity) and further produces a clear delineation of the spinal cord (arrow) in the subarachnoid space. Myelography using MR imaging does not require contrast medium instillation.

collections from any cause (Figure 1—Left), blood collections (Figure 2), deposits of iron-containing compounds and neoplasms (Figure 1—Right).[10-17]

Identifying and characterizing tumors are the most promising of MR imaging uses; a great variety of neoplasms has been examined with an apparently high rate of detection.[7,9,10,13,15] Studies are not yet available to define the false-negative rate for detecting tumor by MR imaging but many investigators estimate that this will be rare. An operator's decisions about the type and number of pulsing sequences may critically affect the sensitivity of MR imaging for detecting tumor.

Disappointingly, available data do not indicate that inherent contrast from MR imaging can reliably differentiate benign from malignant processes. There is wide variation in T1 and T2 times of tumors compared with normal tissues, which themselves vary widely in relaxation characteristics.[9] These overlaps should limit the specificity of MR imaging and may even diminish sensitivity for detecting certain diseases.

Possible Applications for MR Imaging Contrast Media

Modern medicine has several precedents for the augmentation of diagnostic imaging examinations with pharmaceutical contrast enhancers. Examples include barium for gastrointestinal examinations, iodinated organic compounds given intravenously for x-ray urography and computed tomography (CT), myelographic contrast media instilled into the subarachnoid space, radiolabeled compounds for nuclear scintigraphy and, more recently, microsuspensions of air bubbles for echocardiography. With the same intent, researchers are now trying to define pharmaceutical agents that can safely alter the magnetic properties of specific tissues to change the contrast differences for MR imaging.

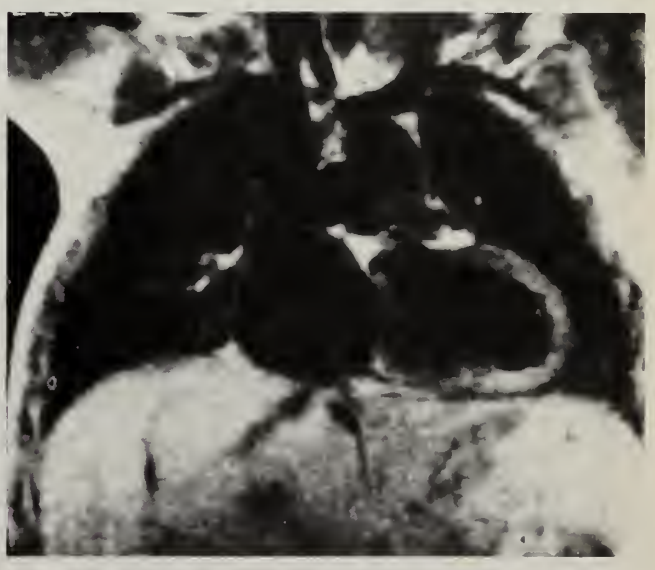

Figure 4.—A coronal image of the heart was obtained by synchronizing the radiofrequency pulses of the imager to the cardiac rhythm. Notice the high contrast between rapidly flowing blood in the heart and great vessels and the myocardium. This child has transposition of the aorta and pulmonary artery.

Certain applications of contrast media already familiar from our experience with x-ray techniques have been obviated by the intrinsic properties of MR imaging. For example, there appears to be little need for a myelographic contrast agent because we can define the subarachnoid space; cardiovascular anatomy can be easily depicted on MR imaging without an intravascular pharmaceutical (Figures 3 and 4).

Magnetic resonance intensity differences, as we have learned, reflect differences in tissue chemistry, which in turn affect T1, T2 and hydrogen density. Motion, as exemplified by rapidly flowing blood, also influences intensity. Yet none of these factors is directly related to tissue function. MR imaging contrast agents distributed on the basis of a particular tissue function would add an important new dimension to MR imaging diagnostic yield.

Familiar examples of function-dependent imaging tests include the intravenous urogram and the contrast-enhanced CT scan of the brain, the latter for assessing the blood-brain-barrier integrity. In parallel fashion, contrast-enhanced function-dependent studies have been shown for MR imaging. MR imaging contrast media injected intravenously can show renal functional abnormalities such as hydronephrosis, ischemia and congestion (Figure 5).[18] The same types of agents can also enhance the sites of blood-brain-barrier disruption.[19,20]

However, MR imaging contrast applications may be able to extend beyond these familiar radiographic applications. Possible applications might include functional assessments of pancreatic tissue, of the brain's metabolic pathways and of liver conjugation pathways. Combining the technologies of monoclonal antibodies and MR imaging contrast media may improve the detection and characterization of malignant lesions and other antigenically distinct pathologic lesions, an exciting possibility for MR imaging contrast investigation.

Mechanism of Paramagnetic Contrast Medium Enhancement

There are important differences between MR imaging contrast agents and iodinated contrast media. The principles of contrast enhancement differ. Radiographic contrast agents, having high electron density, absorb x-rays to produce their contrast effect. MR imaging contrast agents generally belong to a group of chemicals with strong paramagnetic properties; these function by altering local magnetic environments. Paramagnetic contrast agents are not observed directly on the images; rather, their magnetic effects on neighboring hydrogen nuclei are the means of contrast enhancement.[21,22]

All forms of matter possess magnetic properties, a fact described by Faraday in the 19th century. Paramagnetic substances are defined as those that are attracted toward and align with the stronger portion of a magnetic field but, unlike ferromagnetic substances, they return to a random orientation when the magnetic field is removed.[23] When placed in an external magnetic field, paramagnetic agents possess their own local magnetic fields that act as relaxation centers for other nuclei in their microenvironment (Figure 6). The local magnetic field of a paramagnetic molecule shortens the relaxation times of surrounding hydrogen nuclei, a phenomenon called "proton relaxation enhancement."[2] Proton relaxation enhancement shortens T1 and T2 values for neighboring hydrogen nuclei over a short range. This relaxation effect, dependent on the concentration of paramagnetic agents, causes a higher intensity MR signal.[14,21]

Substances are paramagnetic because they possess one or more fundamental particles—proton, neutron or electron—with a spin that is not canceled by another like particle with opposite spin.[23,24] Although there are numerous paramagnetic substances, only a relatively few deserve consideration as possible pharmaceuticals for MR imaging contrast en-

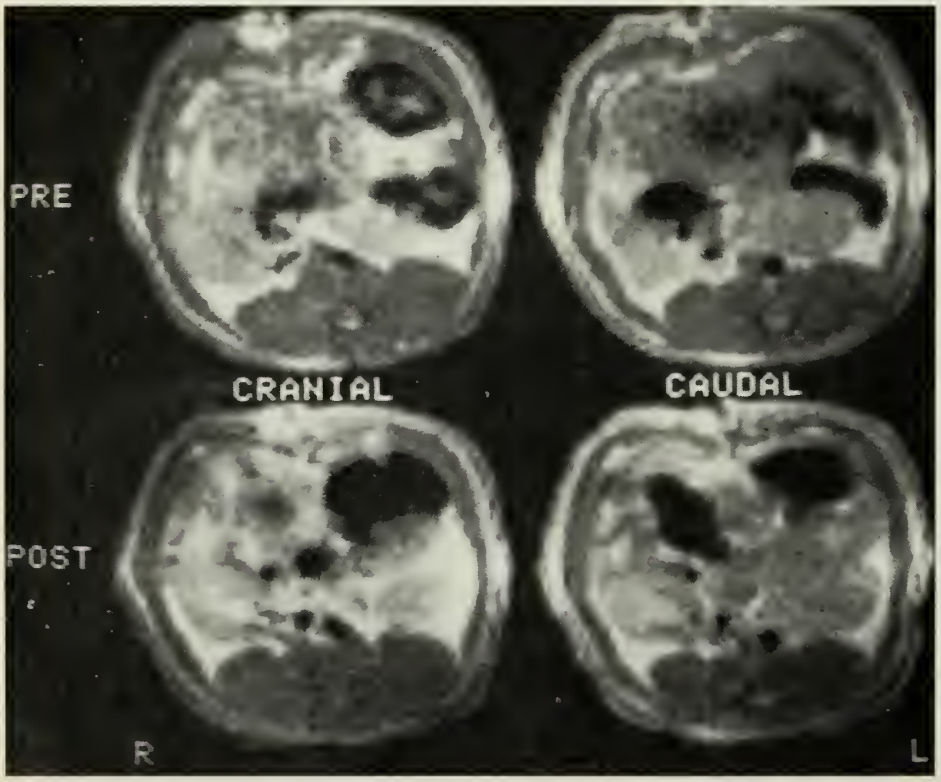

Figure 5.—Contrast-enhanced magnetic resonance images of a rat showing renal functional impairment. Spin-echo images of rat kidneys were obtained before and 15 minutes after administration of a nitroxide spin label (0.5 grams per kg). The precontrast images show equal intensities from the normal right and ischemic left kidney 4 hours after renal artery ligation. The postcontrast images show asymmetric enhancement with increased intensity on the right and no intensity change in the diseased left kidney. (From Brasch et al[18]; reproduced with permission from *Radiology.*)

hancement by virtue of being strongly paramagnetic and being well tolerated by animals. Additional requisites for a paramagnetic contrast agent include stability, wide availability, low cost and appropriate biodistribution and excretion. More than one MR imaging contrast agent, because of different biodistributions, may have clinical efficacy. Yet, all must have low toxicity in doses necessary to produce observable effects on MR images.

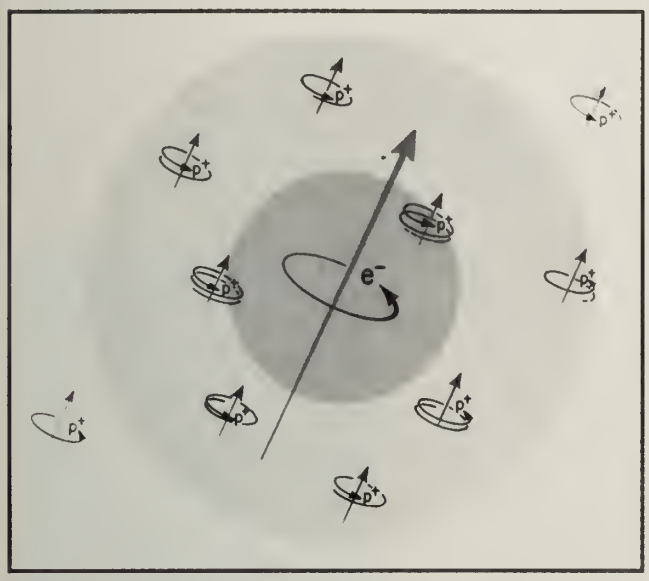

Figure 6.—Proton relaxation enhancement. This schematic of a molecule with a spinning, unpaired electron (symbolized by the large central arrow) depicts the local, microchemical effect (shaded area) of a paramagnetic substance on neighboring hydrogen nuclei (small arrows with unpaired protons). The paramagnetic molecule tends to enhance proton relaxation of nearby hydrogen nuclei and thereby shortens T1 and T2 values. (From Brasch[22]; reproduced with permission from *Radiology*.)

Transition Series Cations		Electron Distribution in 3d Orbitals	Spin Quantum Number
Vo^{+2}	$3d^1$		1/2
Ti^{+2}	$3d^2$		2/2
Cr^{+3}	$3d^3$		3/2
Cr^{+2}, Mn^{+3}	$3d^4$		4/2
Mn^{+2}, Fe^{+3}	$3d^5$		5/2
Fe^{+2}, Co^{+3}	$3d^6$		4/2
Co^{+2}, Ni^{+3}	$3d^7$		3/2
Ni^{+2}, Cu^{+3}	$3d^8$		2/2
Cu^{+2}	$3d^9$		1/2
Cu^{+1}	$3d^{10}$		0

Figure 7.—Electron subshell diagrams of first-transition-series ions are listed with the corresponding spin-quantum numbers. Unpaired electrons with uncanceled spins producing paramagnetic characteristics are shown with single arrows. Electron pairs with zero net spin are depicted by double arrows. Manganous ion (Mn^{+2}) and ferric ion (Fe^{+3}) both contain five unpaired electrons, giving a spin-quantum number of 5/2. Generally, the larger the number of unpaired electrons, the stronger the paramagnetic behavior.

The most powerful paramagnetic agents, and thus those with the greatest proton relaxation enhancement, are substances that contain unpaired electrons (Figure 7). The elements or ions of the periodic table with unpaired electrons are found in the transition series, such as manganese, iron and copper, and lanthanide series, such as gadolinium. A second group of strongly paramagnetic substances are the organic nitroxide stable free radicals, also known as nitroxide spin labels (NSL). These are synthetic organic chemicals that have been used in biomedical research for two decades.[25] Nitroxide spin labels, metals and metal complexes have all been tested as MR imaging contrast agents with some very promising results. Clinical trials using a complex of gadolinium and diethylenetriaminepentaacetic acid (DTPA) are already under way in Europe.[26,27]

Promising Paramagnetics for MR Imaging Contrast Enhancement

In 1978 Lauterbur and co-workers proposed the injection of paramagnetic agents in vivo to change MR imaging tissue contrast; they tried Mn^{+2} as a possible myocardial perfusion agent.[28] Although Mn^{+2} is still being considered for clinical application, the use of free metal ions in humans may be limited by their long retention in the body and a small margin between effective MR imaging dose and toxic dose.

Oral Agents

Although metal ions may not be ideal as intravenously given agents, oral Fe^{+3} (ferric) ions can be used with apparent safety as contrast enhancers for the gastrointestinal tract.[29] Most experts agree that a gastrointestinal contrast enhancer for MR imaging is essential to differentiate bowel from other abdominal structures; this necessity is familiar to those interpreting abdominal CT examinations. Ferric ammonium citrate is the major ingredient in Geritol and has been shown to be safe in a large population as a dietary supplement. A 500-ml dilute solution, 1 mmol, of ferric ammonium citrate has been used effectively for gastrointestinal contrast enhancement on MR imaging (Figure 8), the total dose being

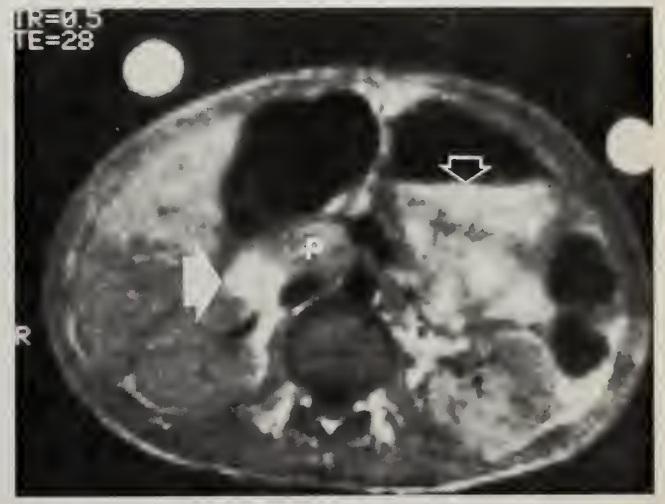

Figure 8.—A spin-echo image of the upper abdomen after oral ingestion of 500 ml of 1 mmol ferric ammonium citrate shows high intensity in the dependent portion of the stomach **(open arrow)** and in the duodenal sweep **(solid arrows)**. The contrast enhancement of the gastrointestinal tract helps to define retroperitoneal structures such as the pancreatic head **(p)**.

less than the usual daily recommended dose of Geritol. Orally administered iron may be the simplest and safest answer to the requirement for abdominal MR imaging; other nonabsorbed paramagnetic formulations may also be effective.[22]

Agents Given Intravenously

Nitroxide spin labels. Many successful MR imaging experiments using nitroxide spin labels have been carried out in our laboratory. The synthetic NSL compounds have increased the diagnostic efficacy of MR imaging for assessing renal function in animals, providing information not available without the use of paramagnetic pharmaceuticals. In animal models of renal artery (see Figure 5) and vein ligation, implanted renal cell carcinoma, unilateral hydronephrosis and acutely infarcted myocardium, enhanced relaxation rates using NSL have been shown.[18] Also, focal disruptions in the blood-brain barrier have been contrast enhanced by intravenously administering NSL.[19] These compounds do not breech the normal blood-brain barrier, but NSLs do accumulate at sites of disease where the barrier has been broken (Figure 9). The least effective diagnostic dose for NSL is less than 0.15 mmol per kg and the median lethal dose (LD_{50}) in rats is about 15 mmol per kg, suggesting a wide margin of safety. Nitroxide spin labels and their metabolites also showed no abnormalities in a sensitive assay of mutagenesis, the sister-chromatid exchange assay.[30] A potentially disadvantageous feature of current nitroxide spin labels is that they can be partially reduced in vivo to nonparamagnetic metabolites. New NSL derivatives with greater in vivo stability, better tolerance and greater relaxation effects are being sought before initiating clinical trials.

Metal complexes. Strongly paramagnetic but relatively toxic metal ions can be largely detoxified by complexation within various chelators. Metal-chelator complexes are being selected to retain strong paramagnetic characteristics but to favor a rapid and complete elimination of the metal from the body. A major challenge confronting the use of intravenously administered metal complexes in biologic systems is the potential for in vivo dissociation of the metal complex, freeing the relatively more toxic metal ion. Thus, selecting metal complexes with high formation constants (K_F) is mandatory. Gadolinium-DTPA is such a compound, with strong relaxing characteristics and rapid and apparently complete biologic elimination.[26]

Of all the paramagnetic cations in the atomic table, gadolinium (Gd^{+3}) has the strongest relaxation rate-enhancing properties. DTPA has a very high formation constant (log $K_F=22$) for Gd^{+3}. The half-life of Gd-DTPA in vivo is 20 minutes with a predominant renal excretion.[26] The LD_{50} in rats is 10 mmol per kg compared with the LD_{50} for noncomplexed gadolinium ions of 0.4 mmol per kg. The effective dose of gadolinium-DTPA for renal contrast enhancement is 0.01 mmol per kg or less, thus suggesting a very high safety index (1 to 1,000).

Gadolinium-DTPA is rapidly distributed in the extracellular fluid space after intravenous administration. It is normally excluded from the brain by the intact blood-brain barrier. However, Gd-DTPA does accumulate at sites of blood-brain-barrier disruption with obvious enhancement of central nervous system lesions including tumors and abscesses (Figure 10).[20,27] Urographic MR imaging experiments using gadolinium-DTPA indicate rapid, easily observable increases in renal parenchymal and renal pelvis signal intensities after intravenous administration of doses as low as 0.01 mmol per kg.[20] This same agent has been shown to be diagnostically

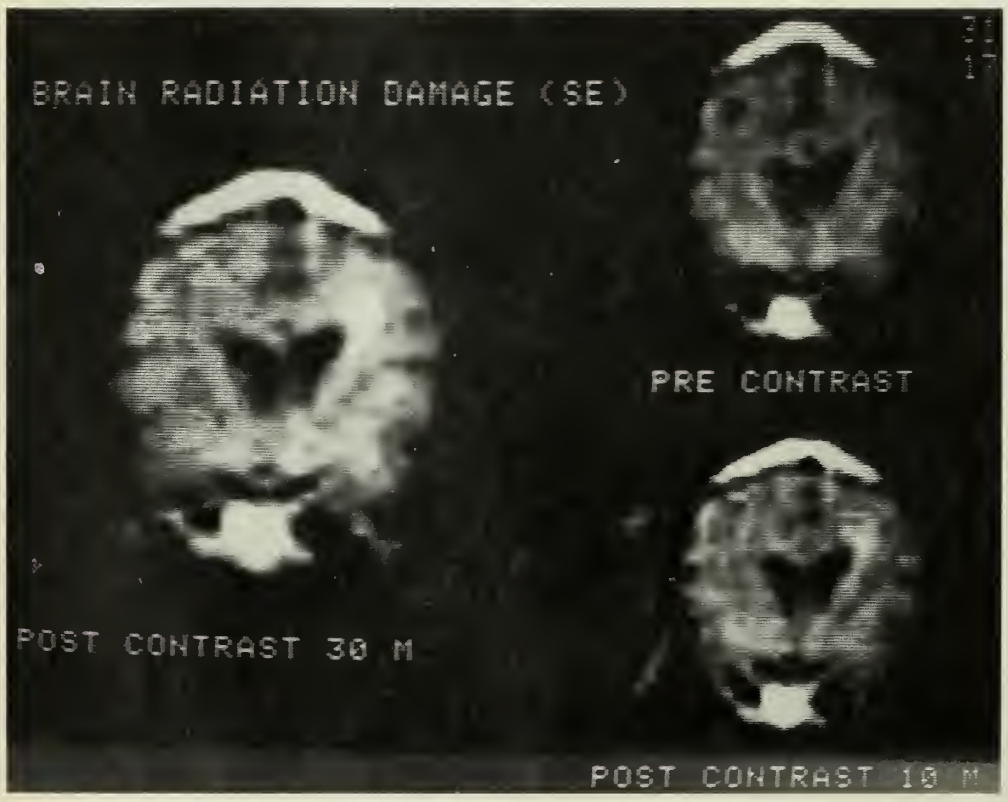

Figure 9.—Nitroxide spin label (NSL)-enhanced cerebral radiation damage. A series of magnetic resonance (MR) images of a dog having radiation-induced brain necrosis before contrast (upper right) and 10 minutes (lower right) and 30 minutes (left) after intravenous administration of NSL (9.9 grams per kg) shows greatly enhanced intensity at the site of brain necrosis. This isomagnetic focus of brain damage was not shown on nonenhanced MR images using pulse-interval times of 0.5 to 1.0 seconds and echo delay times of 28 and 56 ms.

useful in the MR imaging evaluation of sterile abscesses (Figure 11) and of canine myocardial ischemia.[16,20]

On the basis of available data, gadolinium-DTPA appears to be effective not only in experimental animals but in humans.[27] More than 50 patients have received this contrast agent in Europe with no evident toxicity and with striking contrast enhancement of various lesions.[27]

Conclusions

The ultimate role of pharmaceutical contrast enhancement in the MR imaging process is now uncertain, but the possibility of safe, useful agents seems very promising. The manner of administering contrast media is uncertain, in part because the limits of nonenhanced MR imaging are yet to be defined and technologic improvements are still rapidly evolving. However, it appears that contrast media may extend the diagnostic yield of MR imaging and thereby contribute to the general acceptance of this new technique. Accordingly, the development of MR imaging contrast media should parallel, rather than follow, the development of MR imaging instrumentation. Contrast enhancement may be particularly important if the contrast media can shorten the time required to produce with confidence either normal or abnormal imaging examinations. As with all medical decisions, the risk-to-benefit ratio for the use of MR imaging contrast agents will be pivotal.

Figure 10.—Gadolinium-DTPA enhancement of canine radiation-induced necrosis and a surgical wound. Magnetic resonance images before (above) and 25 minutes after (below) intravenous administration of Gd-DTPA (0.5 mmol per kg) show pronounced contrast enhancement of both the surgical hematoma of the scalp and the intracerebral focus of necrosis. (From Brasch et al[20]; reprinted with permission from the *American Journal of Roentgenology.*)

Figure 11.—Abscess and renal enhancement using gadolinium-DTPA. Magnetic resonance images of a rat before and after intravenous administration of Gd-DTPA (0.1 mmol per kg) shows substantial intensity increases in a sterile right flank abscess and in the kidneys due to the local accumulation of the paramagnetic complex. (From Brasch[20]; reprinted with permission from the *American Journal of Roentgenology.*)

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Diagnosis Cluster Frequency in a Community-Based Family Practice Residency Program

Comparison With Large Ambulatory Data Sets

CHARLES L. SHEAR, DrPH, *and* ERIC M. WALL, MD, MPH, *San Bernardino, California*

Ambulatory encounters in a community-based family practice residency program were analyzed using diagnosis clusters. During an 18-month period (July 1982 through December 1983), demographic information and clinical diagnoses for 44,453 successive patient visits were collected and stored in a computerized data base. The 30 most frequent diagnosis clusters accounted for 70% of all recorded clinical diagnoses. Comparison with NAMCS, USC-MAMP (Western Region) and Virginia studies revealed a younger, more indigent population with a higher frequency of visits for hypertension, prenatal and postnatal care, diabetes, chronic respiratory illness and congestive heart failure. Consistent with the other large ambulatory data sets, the general medical examination, hypertension and acute upper respiratory conditions were the most frequent diagnosis clusters. Differences with other reported data sets reflected the site-specific demographic characteristics of patients and providers, regional and environmental influences on the incidence of specific disease states and the relative abundance of other subspecialist physicians. Such local or regional data bases not only provide valuable information as to clinical content but also may help in identifying previously unrecognized health problems.

(Shear CL, Wall EM: Diagnosis cluster frequency in a community-based family practice residency program—Comparison with large ambulatory data sets [Health Care Delivery]. West J Med 1985 Jun; 142:854-857)

Analysis of the clustering of clinical diagnoses according to similar pathophysiologic conditions is a powerful tool to examine the content of ambulatory care. Such clusters purportedly elicit similar cognitive responses in the process of clinical decision making. In their landmark article, Rosenblatt and co-workers[1] have outlined a series of 92 separate diagnosis clusters that (1) encompass the majority of discrete diagnostic entities used in ambulatory practice, (2) decrease the idiosyncratic diagnosis labeling patterns of individual physicians and (3) conform to existing diagnostic classifications used currently in office-based practice.[2]

This technique has thus far been applied to large regional and national data sets that were collected by others and that reflect the content of office-based practice by general and family physicians in the 1970s. The National Ambulatory Medical Care Survey (NAMCS) is an ongoing effort of the National Center for Health Statistics which randomly surveys approximately 1,000 office-based physicians annually. Participating physicians are asked to complete a log-diary of patient encounters during a one-week period at some time from July through October.[3] The Medical Activities and Manpower Project at the University of Southern California (USC-MAMP) study utilized a random sample of physicians identified from the American Medical Association's physician masterfile. A log-diary of each patient encounter during a three-day period was recorded during the summer and fall of 1977.[4] The Virginia Study reported diagnostic data for clinical encounters made between 1973 and 1975 for 36 family physicians and 82 family practice residents practicing in the state of Virginia.[5]

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ABBREVIATIONS USED IN TEXT

COPD = chronic obstructive pulmonary disease
NAMCS = National Ambulatory Medical Care Survey
SBCMC = San Bernardino County Medical Center
USC-MAMP = University of Southern California—Medical Activities and Manpower Project

This study represents an analysis of ambulatory encounters using this technique in a community-based family practice residency program. The goals of this study were to analyze the experience of the first 18 months of an ongoing data base of ambulatory encounters, to validate the usefulness of the technique of diagnosis clusters and to compare the results with those recently reported—keeping in mind that such would reflect only one contemporary training setting for future family physicians.

Methods

The Department of Family Practice of the San Bernardino County Medical Center (SBCMC) presently operates four Family Health Centers in the urban area of San Bernardino County, which is located in the eastern section of the Los Angeles basin. In 1980 the greater San Bernardino metropolitan area had a population of 340,000. Its demographic profile is similar to that of California as a whole, with 82% of the population being white (race) and 19% being of Hispanic origin (ethnicity). Approximately 27% of the population has not completed high school and the median family income is about $20,000. The health status of the county is somewhat lower than that of California as a whole with an age-adjusted death rate of 8.7 per 1,000.

The four Family Health Centers provide the training for 52 family practice residents and the ambulatory care for approximately 32,000 patient visits per year. On July 1, 1982, a computerized system containing clinical and demographic information was initiated. This system is divided into two main data bases. One maintains family-based demographic information on "active patients" (those having made at least one visit to a health center in the preceding 18 months). For each member of a household, the data base includes primary physician name, patient name, age, sex, family relationship code (as indicated on a standard genogram), medical record number and family chart number. The source of information for this data base is registration forms completed by patients at the initial visit to the health center. A second data base maintains diagnostic information on ambulatory encounters at the Family Health Centers and includes the date of the visit as well as the primary and secondary diagnosis for that visit (ICD-9-CM). The source of this information is encounter forms completed by resident and faculty providers. Diagnosis codes (ICD-9-CM) are placed on the encounter forms by clerical personnel and are then verified by the Division of Research before data entry.

Data are entered by trained personnel into a microcomputer with numerous edit traps to improve the accuracy of input information. Periodically, the collected information is sent by telephone to a Harris mainframe computer at Loma Linda University for remote processing by SBCMC personnel. Information on resident patient panels and diagnosis frequency is then regularly distributed to providers and administrative personnel. In addition, when the two data sets are merged, longitudinal information on family utilization of the health centers and diagnostic trends within families can be obtained.

The present report describes the diagnosis clusters for all four Family Health Centers from July 1, 1982, to December 31, 1983. Clusters were constructed from individual ICD-9-CM diagnoses using the method of Schneeweis and co-

TABLE 1.—*Demographic Characteristics of Patient Populations for SBCMC Data Base, NAMCS and USC-MAMP (%)*

Age/Sex Category	SBCMC* (1982-1983)	NAMCS† (1977-1978)	USC-MAMP‡ (1977)
Sex			
Female—all	62.3	59.5	58.4
Male—all	37.7	40.5	41.6
Age (years)			
<17	38.7	18.1	19.1
17-44	38.2	39.1	39.9
45-64	13.8	25.5	24.1
65+	9.2	17.3	16.9

SBCMC=San Bernardino County Medical Center, NAMCS=National Ambulatory Medical Care Survey, USC-MAMP=University of Southern California-Medical Activities and Manpower Project

*Based on age-sex register of 10,733 patients
†Based on 9,164 outpatient encounters.
‡Based on 38,466 outpatient encounters.

TABLE 2.—*Frequency of Diagnosis Clusters in the SBCMC Data Base (July 1982-December 1983)*

Rank	Cluster	Frequency N	Frequency (Cumulative %)
1	Gen. medical examination	7,194	(15.3)
2	Hypertension	3,783	(23.3)
3	Prenatal/postnatal care	3,555	(30.9)
4	Acute upper respiratory tract infection	2,661	(36.5)
5	Diabetes mellitus	2,311	(41.4)
6	Otitis media	1,618	(44.8)
7	Depression/anxiety	1,100	(47.2)
8	Asthma	968	(49.2)
9	Emphysema, COPD	900	(51.1)
10	Urinary tract infection	793	(52.8)
11	Soft tissue injury	698	(54.3)
12	Degenerative joint disease	636	(55.7)
13	Ischemic heart disease	622	(57.0)
14	Congestive heart failure	619	(58.2)
15	Abdominal pain	515	(59.4)
16	Nonfungal skin infection	512	(60.5)
17	Vaginitis/vulvitis	510	(61.6)
18	Contraception	377	(62.4)
19	Headaches	374	(63.2)
20	Peptic diseases	367	(63.9)
21	Acute lower respiratory tract infection	334	(64.6)
22	Fibrositis, myalgia	318	(65.3)
23	Thyroid disease	306	(66.0)
24	Dermatitis, eczema	305	(66.6)
25	Conjunctivitis, keratitis	302	(67.3)
26	Rheumatoid disease	278	(67.9)
27	Chest pain	260	(68.4)
28	Menstrual disorders	255	(68.9)
29	Sprains, strains	243	(69.5)
30	Seizure disorder	235	(70.0)

COPD=chronic obstructive pulmonary disease

workers.[2] Only primary diagnoses were used in the construction of these clusters. These represent 95% of all diagnoses recorded during this time.

Results

In all, 10,733 persons were identified as active patients during the period July 1, 1982, through December 31, 1983. Approximately 60% of these were female. Nearly 40% of the practice population was under 17 years of age with 10% over age 65; 51% of patients were white, 32% Hispanic and 13% black. As seen in Table 1 this population is considerably younger than those of the NAMCS and USC-MAMP studies. More than 85% of the SBCMC population receive Medi-Cal or Medicare assistance.

The ten most frequent diagnosis clusters represented 52.8% of the 44,453 primary diagnoses made during the study period with the top 30 clusters accounting for 70% of all diagnoses (Table 2). The general medical examination, hypertension and prenatal and postnatal care were the most frequent clusters accounting for approximately a third of all diagnoses made.

Comparison with other studies (see Table 3) indicates a higher frequency of hypertension, prenatal and postnatal care, diabetes mellitus, otitis media, asthma, emphysema, COPD (chronic obstructive pulmonary disease)-bronchitis, congestive heart failure and contraception in the SBCMC population. Notably less frequent were acute orthopedic injuries such as sprains, strains, soft tissue injury, fractures and dislocations. Rhinitis, sinusitis and acute lower respiratory tract infections were much less frequent than reported in other studies. Finally, obesity, infectious diarrhea/gastroenteritis and medical/surgical aftercare were significantly lower in frequency in the SBCMC data base.

Discussion

The results of this study confirm the ability of diagnosis clusters to effectively reduce the quantity of diagnostic information into a more manageable and meaningful number. In the SBCMC data base, 70% of all diagnoses were captured in the 30 most frequent clusters. This is comparable to the experience of Schneeweis and associates.[2] Independent of the method of data collection, three diagnosis clusters have been found consistently in all reported ambulatory data sets. These include the general medical examination, hypertension and acute upper respiratory tract conditions. These three will account for approximately 25% to 30% of all diagnoses.

The diverse spectrum of clinical diagnoses encountered in family practice is also seen in this study. Those factors influencing this spectrum include the demographic characteristics of patients and physicians, the incidence of specific disease states, the relative supply of other physician specialists and the focus or setting of care.[1] The SBCMC data reported here are from one residency training setting where the majority of physicians are 25 to 32 years of age. This may have influenced the age distribution of the patient population which has twice as many persons younger than 17 years as the NAMCS and USC-MAMP studies. This age difference may explain in part the high relative frequency of prenatal and postnatal care, otitis media and contraception.

The high relative frequency of hypertension, diabetes and congestive heart failure at first seems inconsistent with this younger population. On the other hand, socioeconomic and

TABLE 3.—*Most Frequent Diagnosis Clusters Encountered at SBCMC and Comparison With USC-MAMP, NAMCS and Virginia Studies*

Diagnosis Cluster	SBCMC*		USC-MAMP†		NAMCS‡		Virginia§	
	Rank	%	Rank	%	Rank	%	Rank	%
General medical examination	1	(15.3)	1	(12.2)	1	(9.8)	1	(11.7)
Hypertension	2	(7.9)	3	(4.8)	3	(6.8)	3	(5.8)
Prenatal and postnatal care	3	(7.5)	6	(3.3)	7	(2.9)	13	(1.5)
Acute upper respiratory tract infection	4	(5.6)	2	(7.5)	2	(9.3)	2	(8.4)
Diabetes mellitus	5	(4.9)	9	(1.9)	9	(2.4)	8	(2.4)
Otitis media	6	(3.4)	21	(1.1)	17	(1.4)	11	(1.9)
Depression/anxiety	7	(2.3)	7	(2.7)	10	(2.3)	6	(3.8)
Asthma	8	(2.1)	>25		29	(0.7)	>30	
Emphysema, COPD	9	(1.9)	20	(1.3)	>30		>30	
Urinary tract infection	10	(1.7)	15	(1.5)	16	(1.7)	17	(1.2)
Soft tissue injury	11	(1.5)	5	(4.2)	4	(4.2)	4	(4.0)
Degenerative joint disease	12	(1.4)	10	(1.8)	13	(2.1)	15	(1.4)
Ischemic heart disease	13	(1.3)	14	(1.5)	8	(2.5)	9	(2.2)
Congestive heart failure	14	(1.3)	>25		>30		>30	
Abdominal pain	15	(1.1)	>25		>30		>30	
Nonfungal skin infections	16	(1.1)	24	(0.9)	20	(1.2)	12	(1.7)
Vaginitis/vulvitis	17	(1.1)	11	(1.8)	23	(1.1)	16	(1.2)
Contraception	18	(0.8)	>25		>30		>30	
Headaches	19	(0.8)	23	(1.1)	27	(0.7)	24	(0.8)
Peptic diseases	20	(0.8)	22	(1.1)	21	(1.2)	22	(0.9)

SBCMC=San Bernardino County Medical Center, USC-MAMP=University of Southern California-Medical Activities and Manpower Project, NAMCS=National Ambulatory Medical Care Survey, COPD=chronic obstructive pulmonary disease

*Based on 44,453 outpatient encounters (1982-1983).
†Based on Western Region encounters only (1977).
‡Based on 9,164 outpatient encounters (1977-1978).
§Based on 526,196 encounters (1973-1975).

ethnic factors may well be influential in determining the content of practice in this setting. Most of these patients receive medical entitlement benefits and approximately a third are of Hispanic descent. It is significant that this latter group has been found to be at particularly high risk for diabetes mellitus.[6]

A higher frequency of obesity would be expected in view of the increased visits reported for diabetes and heart disease. No such association was found in this study, perhaps because physicians recorded this as a secondary diagnosis. If this is true, it suggests that this training setting fails to adequately address the importance of this problem.

The influence of a relative abundance of other specialists may also explain some of the results. The low frequency of acute orthopedic injuries, for example, may be a result of the presence of appropriate subspecialty services and an emergency room department available in the same institution.

Finally, the influence of environmental conditions on clinical content is strongly supported by the SBCMC data. The very high visit rates for emphysema, COPD, bronchitis and asthma may be explained by the poor air quality of the Los Angeles basin which characteristically worsens from May through October. Preliminary analysis of cluster frequency by month lends support to this hypothesis. Further investigation of this phenomenon is planned at a later date.

In conclusion, the results of this study put into perspective the reports of national versus regional encounter data sets. While large national data bases do give an accurate estimate of national trends, the application of these findings to local practices and training settings must be viewed with some skepticism. Local influences of training, physician supply, environment and characteristics of patients and providers may dramatically determine the clinical content of such encounters. Consequently, it is recommended that similar data bases be developed locally or regionally so that family practice residency programs can more accurately determine the proper balance of clinical content appropriate for their needs and goals. The availability of such information to community physicians may also serve an important function in identifying local health problems that otherwise would go unnoticed.

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In Memoriam

California Medical Association

ANDERSON, WILLIAM L., San Francisco. Died January 21, 1985, in San Mateo, aged 64. Graduate of Utah College of Medicine, Salt Lake City, 1944. Licensed in California in 1945. Dr Anderson was a member of the San Francisco Medical Association.

ARTHUR, JAMES, M., Fresno. Died January 26, 1985, aged 76. Graduate of Baylor University College of Medicine, Houston, 1936. Licensed in California in 1936. Dr Arthur was a retired member of the Fresno-Madera Medical Society.

BENNETT, ABRAM E., Berkeley. Died March 7, 1985, in Berkeley, aged 87. Graduate of the University of Nebraska College of Medicine, Omaha, 1921. Licensed in California in 1947. Dr Bennett was a retired member of the Alameda-Contra Costa Medical Association.

BRIGNALL, GAYLORD W., Stockton. Died March 14, 1985, aged 79. Graduate of the College of Osteopathic Physicians and Surgeons, Los Angeles, 1935. Licensed in California in 1936. Dr Brignall was a retired member of the San Joaquin County Medical Society.

CABAUD, HENRY EDWARD III, San Francisco. Died January 11, 1985, of cancer, aged 40. Graduate of the University of Southern California School of Medicine, Los Angeles, 1970. Licensed in California in 1971. Dr Cabaud was a member of the San Francisco Medical Society.

COHN, ALBERT, Vallejo. Died January 15, 1985, aged 86. Graduate of Ludwig-Maximillians-Universität, Medizinische Fakultät, München, 1924. Licensed in California in 1942. Dr Cohn was a retired member of the Solano County Medical Association.

DURAND, ROBERT L., San Francisco. Died February 27, 1985, in San Francisco, aged 64. Graduate of St Louis University School of Medicine, St Louis, 1945. Licensed in California in 1945. Dr Durand was a member of the San Francisco Medical Society.

GAECKLE, DUDLEY JAMES, Pleasanton. Died January 12, 1985, in Pleasanton, aged 53. Graduate of the University of California School of Medicine, Berkeley-San Francisco, 1956. Licensed in California in 1957. Dr Gaeckle was a retired member of the Alameda-Contra Costa Medical Association.

HART, WINFRED E., Oakland. Died January 13, 1985, aged 86. Graduate of Western Reserve University School of Medicine, Cleveland, 1928. Licensed in California in 1929. Dr Hart was a retired member of the Alameda-Contra Costa Medical Association.

HOOVER, HAROLD R., Whittier. Died January 12, 1985, in Newport Beach, aged 72. Graduate of the University of Southern California School of Medicine, Los Angeles, 1938. Licensed in California in 1938. Dr Hoover was a retired member of the Los Angeles County Medical Association.

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PETZOLDT, RICHARD L., San Jose. Died March 1, 1985, in San Jose, aged 52. Graduate of the University of California School of Medicine, San Francisco, 1966. Licensed in California in 1967. Dr Petzoldt was a member of the Santa Clara County Medical Society.

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SAMSON, HUGH R. G., Santa Ana. Died February 21, 1985, aged 63. Graduate of Western Ontario Faculty of Medicine, London, 1945. Licensed in California in 1966. Dr Samson was a member of the Orange County Medical Association.

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STRANG, THEODORE A., Long Beach. Died February 4, 1985, in Long Beach, aged 82. Graduate of Northwestern University Medical School, Chicago, 1926. Licensed in California in 1927. Dr Strang was a retired member of the Los Angeles County Medical Association.

WOO, HENRY B., San Francisco. Died December 17, 1984, in San Francisco, aged 77. Graduate of George Washington University School of Medicine, Washington, DC, 1933. Licensed in California in 1935. Dr Woo was a member of the San Francisco Medical Society.

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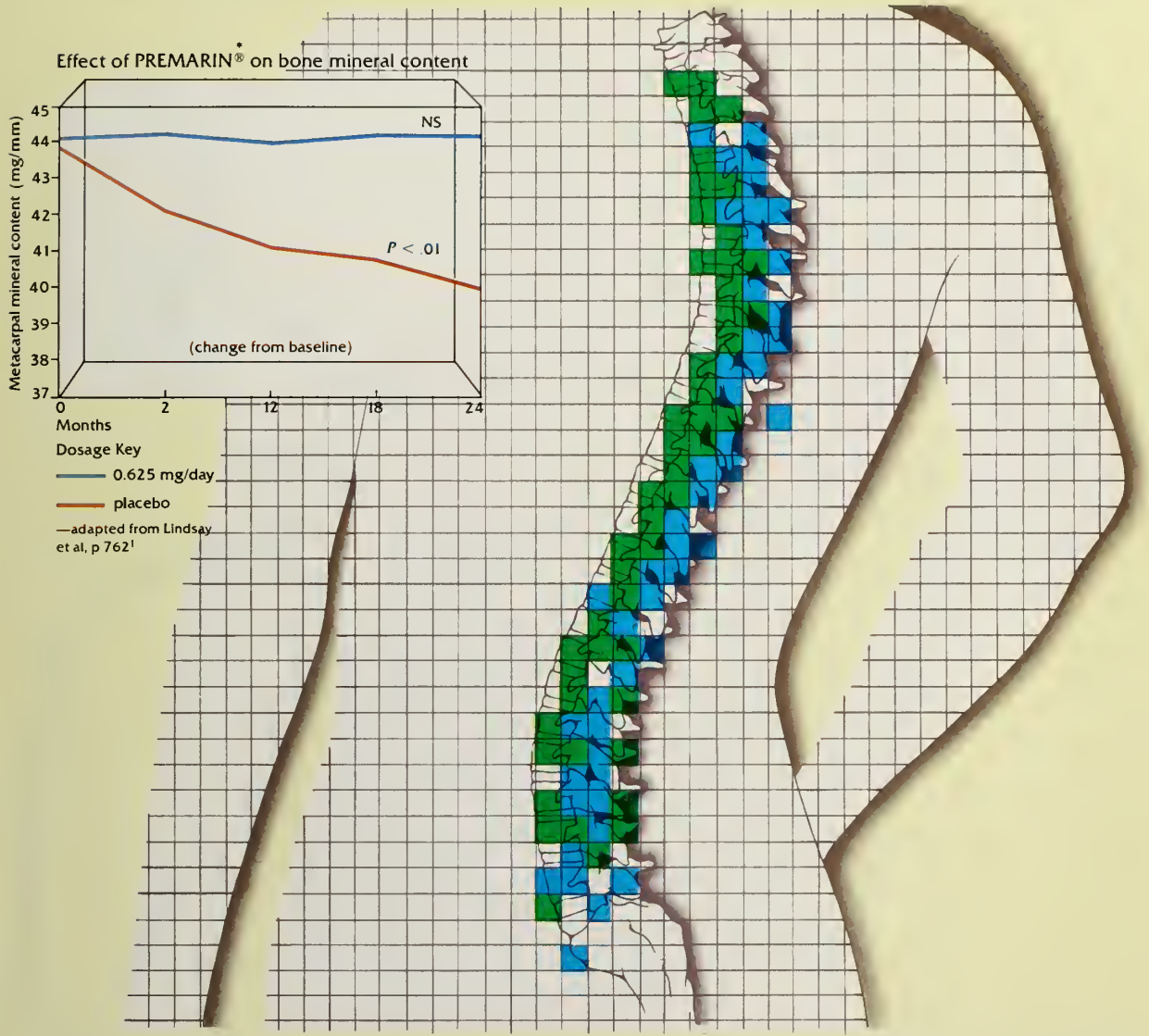
POSTMENOPAUSAL BONE LOSS THAT INCAPACITATES

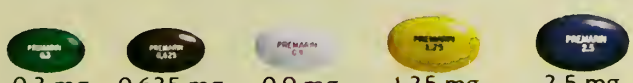


PREMARIN MAY HALT THE DISABLING COURSE OF OSTEOPOROSIS*

Osteoporosis has an enormous epidemiological impact: it affects 10 million American women, and 26% of all women over age 60.[2] The disease begins silently and progresses inexorably for 15 to 20 years, until disabling complications occur.[3]

To minimize osteoporotic damage, the condition must be detected early and treated promptly. For many patients, PREMARIN is optimal therapy for osteoporosis, as part of a comprehensive program that includes exercise, good nutrition, and calcium supplements. In a controlled study of postmenopausal and oophorectomized women, PREMARIN (Conjugated Estrogens Tablets, U.S.P.) doses of 0.625 mg/day prevented loss of metacarpal mineral content (see graph above).

PREMARIN®
(CONJUGATED ESTROGENS TABLETS, U.S.P.)



0.3 mg 0.625 mg 0.9 mg 1.25 mg 2.5 mg

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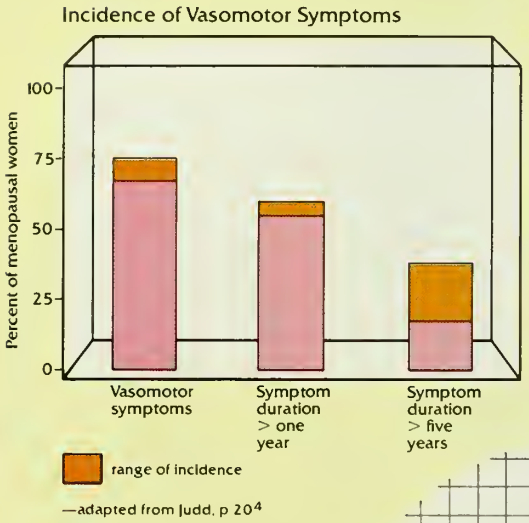
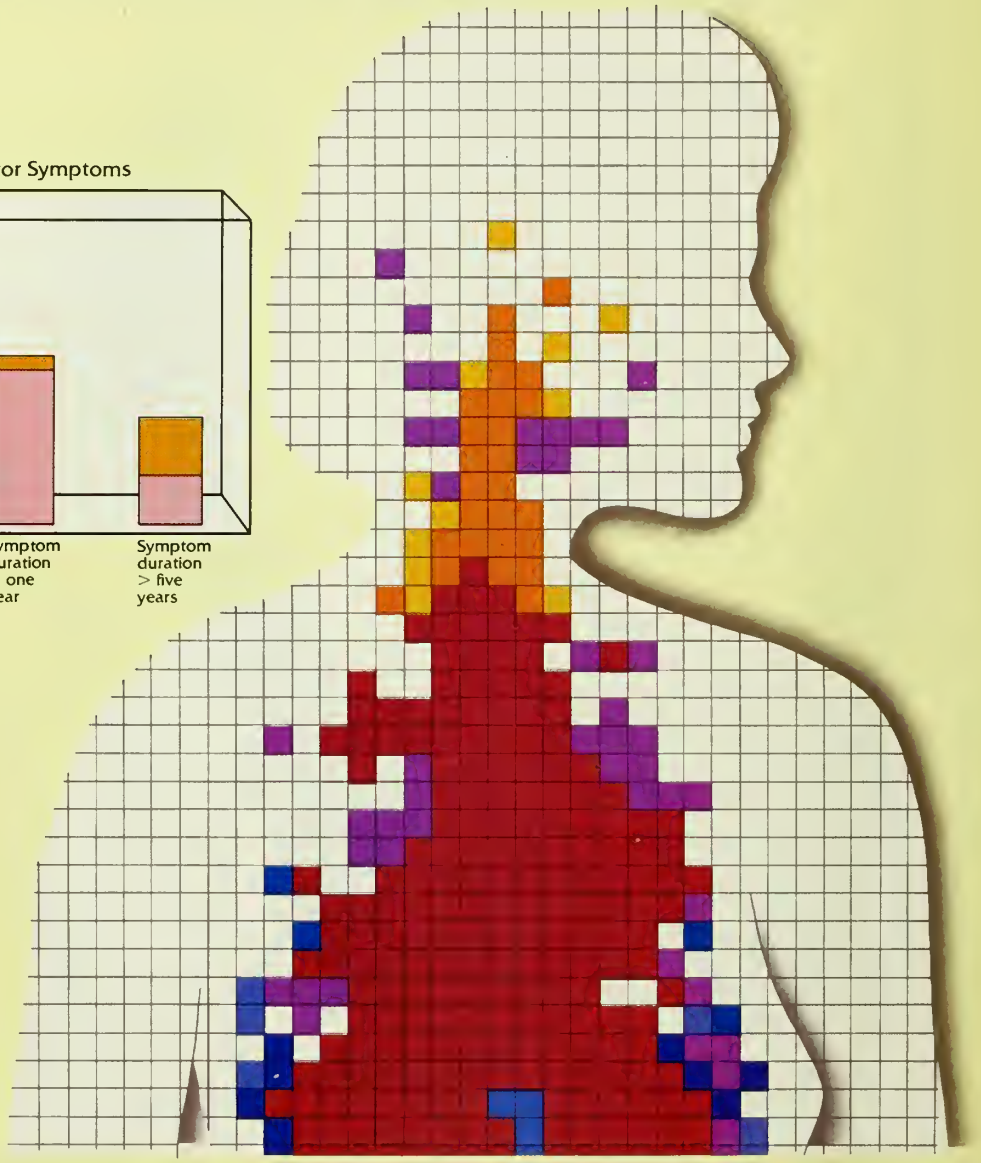
*Conjugated Estrogens Tablets have been evaluated as probably effective for estrogen-deficiency-induced osteoporosis.

Please see last page for brief summary of full prescribing information.

VASOMOTOR SYMPTOMS THAT DEMAND INTERVENTION





PREMARIN RELIEVES MODERATE TO SEVERE VASOMOTOR SYMPTOMS

Vasomotor symptoms are the most common manifestation of the menopause, affecting up to 75% of menopausal women. Of these, 80% may suffer for more than a year and up to 50% for more than five years.[4] These symptoms can disrupt a woman's life by chronically interrupting sleep, resulting in anxiety and irritability.

In a study of postmenopausal women suffering severe episodes of cutaneous flushing, symptoms improved markedly after administration of estrogen[5]—the treatment of choice for moderate to severe vasomotor symptoms.[6] The estrogen of choice is PREMARIN, the most widely prescribed estrogen for over 40 years. PREMARIN (Conjugated Estrogens Tablets, U.S.P.) relieves moderate to severe vasomotor symptoms of the natural menopause, as well as the acute and often severe symptoms of surgical menopause.

PREMARIN®

(CONJUGATED ESTROGENS TABLETS, U.S.P.)

0.3 mg 0.625 mg 0.9 mg 1.25 mg 2.5 mg

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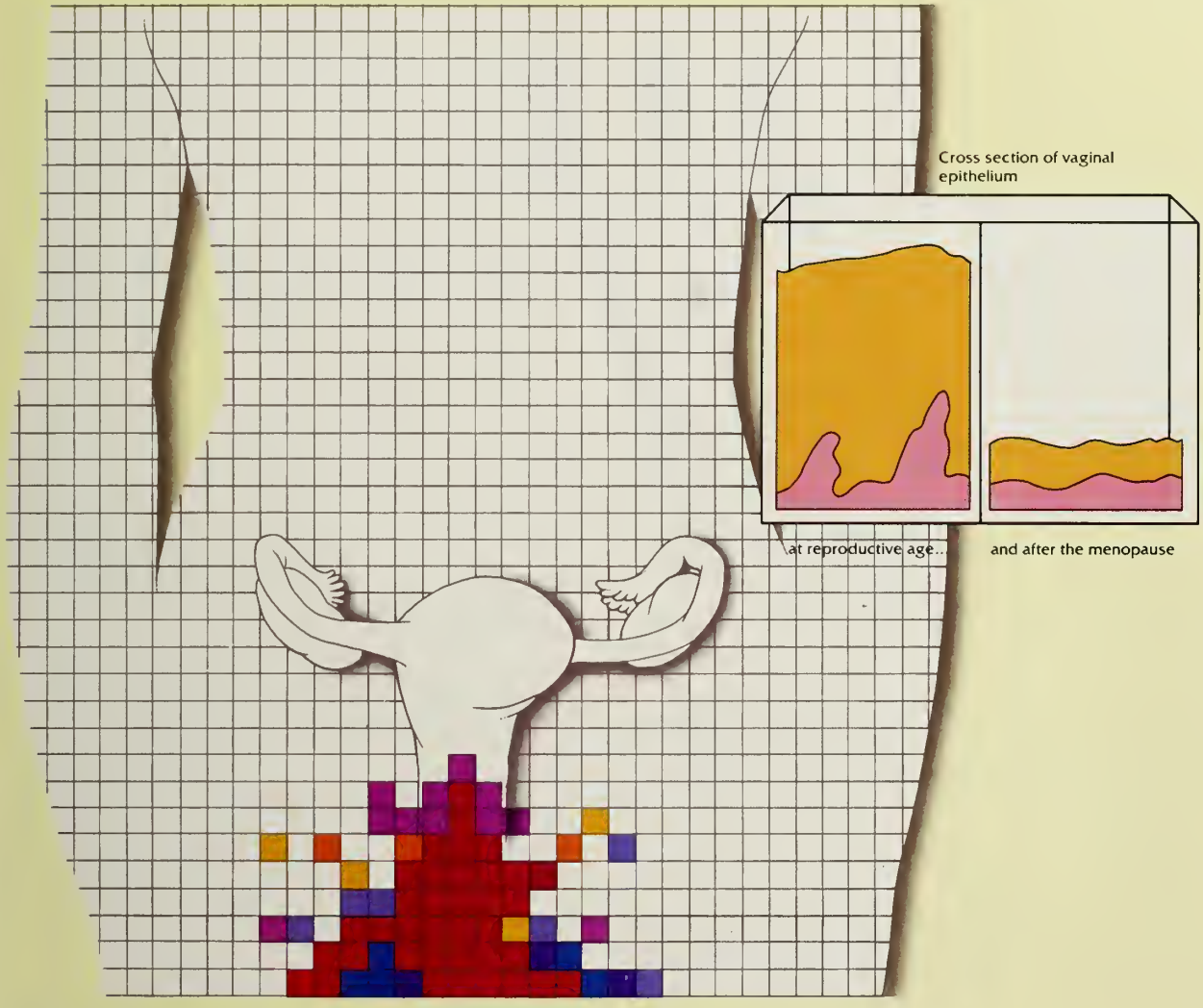
VAGINAL ATROPHY THAT INTERFERES WITH SEXUALITY



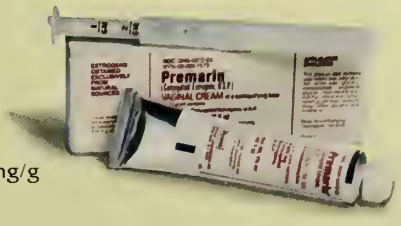
PREMARIN RESTORES THE VAGINAL ENVIRONMENT

In the postmenopausal woman, decreasing levels of estrogen can have devastating effects on a woman's sexual functioning. The pH of vaginal secretions rises, promoting the growth of contaminating organisms. The vaginal epithelium dries and thins, becoming susceptible to irritation, injury, and infection. Sexual relations may be difficult or impossible.

PREMARIN (Conjugated Estrogens, U.S.P.) Vaginal Cream focuses therapy at the site of the problem. Vaginal dryness is relieved, pH reverts to its normal acidity, and the epithelium thickens and becomes more resistant to injury and infection. With the vaginal environment returned to its premenopausal state, sexual function may improve.

PREMARIN®

(CONJUGATED ESTROGENS, U.S.P.) Vaginal Cream



0.625 mg/g

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BRIEF SUMMARY *(FOR FULL PRESCRIBING INFORMATION AND PATIENT INFORMATION, SEE PACKAGE CIRCULAR)*

PREMARIN® Brand of Conjugated Estrogens Tablets, U.S.P.
PREMARIN® Brand of Conjugated Estrogens, U.S.P. Vaginal Cream in a nonliquefying base

1. ESTROGENS HAVE BEEN REPORTED TO INCREASE THE RISK OF ENDOMETRIAL CARCINOMA

Three independent case control studies have reported an increased risk of endometrial cancer in postmenopausal women exposed to exogenous estrogens for more than one year. This risk was independent of the other known risk factors for endometrial cancer. These studies are further supported by the finding that incidence rates of endometrial cancer have increased sharply since 1969 in eight different areas of the United States with population-based cancer reporting systems, an increase which may be related to the rapidly expanding use of estrogens during the last decade. The three case control studies reported that the risk of endometrial cancer in estrogen users was about 4.5 to 13.9 times greater than in nonusers. The risk appears to depend on both duration of treatment and on estrogen dose. In view of these findings, when estrogens are used for the treatment of menopausal symptoms, the lowest dose that will control symptoms should be utilized and medication should be discontinued as soon as possible. When prolonged treatment is medically indicated, the patient should be reassessed on at least a semiannual basis to determine the need for continued therapy. Although the evidence must be considered preliminary, one study suggests that cyclic administration of low doses of estrogen may carry less risk than continuous administration; it therefore appears prudent to utilize such a regimen. Close clinical surveillance of all women taking estrogens is important. In all cases of undiagnosed persistent or recurring abnormal vaginal bleeding, adequate diagnostic measures should be undertaken to rule out malignancy. There is no evidence at present that "natural" estrogens are more or less hazardous than "synthetic" estrogens at equiestrogenic doses.

2. ESTROGENS SHOULD NOT BE USED DURING PREGNANCY

The use of female sex hormones, both estrogens and progestogens, during early pregnancy may seriously damage the offspring. It has been shown that females exposed in utero to diethylstilbestrol, a non-steroidal estrogen, have an increased risk of developing in later life a form of vaginal or cervical cancer that is ordinarily extremely rare. This risk has been estimated as not greater than 4 per 1000 exposures. Furthermore, a high percentage of such exposed women (from 30 to 90 percent) have been found to have vaginal adenosis, epithelial changes of the vagina and cervix. Although these changes are histologically benign, it is not known whether they are precursors of malignancy. Although similar data are not available with the use of other estrogens, it cannot be presumed they would not induce similar changes. Several reports suggest an association between intrauterine exposure to female sex hormones and congenital anomalies, including congenital heart defects and limb reduction defects. One case control study estimated a 4.7-fold increased risk of limb reduction defects in infants exposed in utero to sex hormones (oral contraceptives, hormone withdrawal tests for pregnancy, or attempted treatment for threatened abortion). Some of these exposures were very short and involved only a few days of treatment. The data suggest that the risk of limb reduction defects in exposed fetuses is somewhat less than 1 per 1000. In the past, female sex hormones have been used during pregnancy in an attempt to treat threatened or habitual abortion. There is considerable evidence that estrogens are ineffective for these indications, and there is no evidence from well controlled studies that progestogens are effective for these uses. If PREMARIN is used during pregnancy, or if the patient becomes pregnant while taking this drug, she should be apprised of the potential risks to the fetus, and the advisability of pregnancy continuation.

DESCRIPTION: PREMARIN (Conjugated Estrogens, U.S.P.) contains a mixture of estrogens, obtained exclusively from natural sources, blended to represent the average composition of material derived from pregnant mares' urine. It contains estrone, equilin, and 17α-dihydroequilin, together with smaller amounts of 17α-estradiol, equilenin, and 17α-dihydroequilenin as salts of their sulfate esters.

INDICATIONS: Based on a review of PREMARIN Tablets by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications for use as follows:

Effective: 1. Moderate to severe vasomotor symptoms associated with the menopause. (There is no evidence that estrogens are effective for nervous symptoms or depression without associated vasomotor symptoms, and they should not be used to treat such conditions.)

2. Atrophic vaginitis
3. Kraurosis vulvae
4. Female hypogonadism
5. Female castration
6. Primary ovarian failure
7. Breast cancer (for palliation only) in appropriately selected women and men with metastatic disease.
8. Prostatic carcinoma—palliative therapy of advanced disease.
9. Postpartum breast engorgement—Although estrogens have been widely used for the prevention of postpartum breast engorgement, controlled studies have demonstrated that the incidence of significant painful engorgement in patients not receiving such hormonal therapy is low and usually responsive to appropriate analgesic or other supportive therapy. Consequently, the benefit to be derived from estrogen therapy for this indication must be carefully weighed against the potential increased risk of puerperal thromboembolism associated with the use of large doses of estrogens.

PREMARIN HAS NOT BEEN SHOWN TO BE EFFECTIVE FOR ANY PURPOSE DURING PREGNANCY AND ITS USE MAY CAUSE SEVERE HARM TO THE FETUS (SEE BOXED WARNING).

"Probably" effective: For estrogen deficiency-induced osteoporosis, and only when used in conjunction with other important therapeutic measures such as diet, calcium, physiotherapy, and good general health-promoting measures. Final classification of this indication requires further investigation.

INDICATIONS: PREMARIN (Conjugated Estrogens, U.S.P.) Vaginal Cream is indicated in the treatment of atrophic vaginitis and kraurosis vulvae. PREMARIN Vaginal Cream HAS NOT BEEN SHOWN TO BE EFFECTIVE FOR ANY PURPOSE DURING PREGNANCY AND ITS USE MAY CAUSE SEVERE HARM TO THE FETUS (SEE BOXED WARNING).

CONTRAINDICATIONS: Estrogens should not be used in women (or men) with any of the following conditions: 1. Known or suspected cancer of the breast except in appropriately selected patients being treated for metastatic disease. 2. Known or suspected estrogen-dependent neoplasia. 3. Known or suspected pregnancy (See Boxed Warning). 4. Undiagnosed abnormal genital bleeding. 5. Active thrombophlebitis or thromboembolic disorders. 6. A past history of thrombophlebitis, thrombosis, or thromboembolic disorders associated with previous estrogen use (except when used in treatment of breast or prostatic malignancy).

WARNINGS: Long term continuous administration of natural and synthetic estrogens in certain animal species increases the frequency of carcinomas of the breast, cervix, vagina, and liver. There are now reports that estrogens increase the risk of carcinoma of the endometrium in humans. (See Boxed Warning.) At the present time there is no satisfactory evidence that estrogens given to postmenopausal women increase the risk of cancer of the breast, although a recent study has raised this possibility. There is a need for caution in prescribing estrogens for women with a strong family history of breast cancer or who have breast nodules, fibrocystic disease, or abnormal mammograms. A recent study has reported a 2- to 3-fold increase in the risk of surgically confirmed gallbladder disease in women receiving postmenopausal estrogens.

Adverse effects of oral contraceptives may be expected at the larger doses of estrogen used to treat prostatic or breast cancer or postpartum breast engorgement, it has been shown that there is an increased risk of thrombosis in men receiving estrogens for prostatic cancer and women for postpartum breast engorgement. Users of oral contraceptives have an increased risk of diseases, such as thrombophlebitis, pulmonary embolism, stroke, and myocardial infarction. Cases of retinal thrombosis, mesenteric thrombosis, and optic neuritis have been reported in oral contraceptive users. An increased risk of postsurgery thromboembolic complications has also been reported in users of oral contraceptives. If feasible, estrogen should be discontinued at least 4 weeks before surgery of the type associated with an increased risk of thromboembolism, or during periods of prolonged immobilization. Estrogens should not be used in persons with active thrombophlebitis, thromboembolic disorders, or in persons with a history of such disorders in association with estrogen use. They should be used with caution in patients with cerebral vascular or coronary artery disease. Large doses (5 mg conjugated estrogens per day), comparable to those used to treat cancer of the prostate and breast have been shown to increase the risk of nonfatal myocardial infarction, pulmonary embolism and thrombophlebitis. When doses of this size are used, any of the thromboembolic and thrombotic adverse effects should be considered a clear risk.

Benign hepatic adenomas should be considered in estrogen users having abdominal pain and tenderness, abdominal mass, or hypovolemic shock. Hepatocellular carcinoma has been reported in women taking estrogen-containing oral contraceptives. Increased blood pressure may occur with use of estrogens in the menopause and blood pressure should be monitored with estrogen use. A worsening of glucose tolerance has been observed in patients on estrogen-containing oral contraceptives. For this reason, diabetic patients should be carefully observed. Estrogens may lead to severe hypercalcemia in patients with breast cancer and bone metastases.

PRECAUTIONS: Physical examination and a complete medical and family history should be taken prior to the initiation of any estrogen therapy with special reference to blood pressure, breasts, abdomen, and pelvic organs, and should include a Papanicolau smear. As a general rule, estrogen should not be prescribed for longer than one year without another physical examination being performed. Conditions influenced by fluid retention such as asthma, epilepsy, migraine, and cardiac or renal dysfunction, require careful observation. Certain patients may develop manifestations of excessive estrogenic stimulation, such as abnormal or excessive uterine bleeding, mastodynia, etc. Prolonged administration of unopposed estrogen therapy has been reported to increase the risk of endometrial hyperplasia in some patients. Oral contraceptives appear to be associated with an increased incidence of mental depression. Patients with a history of depression should be carefully observed. Preexisting uterine leiomyomata may increase in size during estrogen use. The pathologist should be advised of estrogen therapy when relevant specimens are submitted. If jaundice develops in any patient receiving estrogen, the medication should be discontinued while the cause is investigated. Estrogens should be used with care in patients with impaired liver function, renal insufficiency, metabolic bone diseases associated with hypercalcemia, or in young patients in whom bone growth is not complete.

The following changes may be expected with larger doses of estrogen:

a. Increased sulfobromophthalein retention.
b. Increased prothrombin and factors VII, VIII, IX, and X; decreased antithrombin 3, increased norepinephrine-induced platelet aggregability.
c. Increased thyroid binding globulin (TBG) leading to increased circulating total thyroid hormone, as measured by PBI, T4 by column, or T4 by radioimmunoassay. Free T3 resin uptake is decreased, reflecting the elevated TBG; free T4 concentration is unaltered.
d. Impaired glucose tolerance.
e. Decreased pregnanediol excretion.
f. Reduced response to metyrapone test.
g. Reduced serum folate concentration.
h. Increased serum triglyceride and phospholipid concentration.

As a general principle, the administration of any drug to nursing mothers should be done only when clearly necessary since many drugs are excreted in human milk.

ADVERSE REACTIONS: The following have been reported with estrogenic therapy, including oral contraceptives: breakthrough bleeding, spotting, change in menstrual flow; dysmenorrhea; premenstrual-like syndrome; amenorrhea during and after treatment; increase in size of uterine fibromyomata; vaginal candidiasis, change in cervical erosion and in degree of cervical secretion; cystitis-like syndrome; tenderness, enlargement, secretion (of breasts); nausea, vomiting, abdominal cramps, bloating; cholestatic jaundice; chloasma or melasma which may persist when drug is discontinued; erythema multiforme; erythema nodosum; hemorrhagic eruption; loss of scalp hair, hirsutism; steepening of corneal curvature; intolerance to contact lenses; headache, migraine, dizziness, mental depression, chorea; increase or decrease in weight; reduced carbohydrate tolerance; aggravation of porphyria; edema; changes in libido.

ACUTE OVERDOSAGE: May cause nausea, and withdrawal bleeding may occur in females.

DOSAGE AND ADMINISTRATION:

PREMARIN® Brand of Conjugated Estrogens Tablets, U.S.P.

1. *Given cyclically for short-term use only.* For treatment of moderate to severe vasomotor symptoms, atrophic vaginitis, or kraurosis vulvae associated with the menopause (0.3 to 1.25 mg or more daily).

The lowest dose that will control symptoms should be chosen and medication should be discontinued as promptly as possible.

Administration should be cyclic (e.g., three weeks on and one week off).

Attempts to discontinue or taper medication should be made at three to six month intervals.

2. *Given cyclically:* Female hypogonadism. Female castration. Primary ovarian failure. Osteoporosis.

Female hypogonadism—2.5 to 7.5 mg daily, in divided doses for 20 days, followed by a rest period of 10 days' duration. If bleeding does not occur by the end of this period, the same dosage schedule is repeated. The number of courses of estrogen therapy necessary to produce bleeding may vary depending on the responsiveness of the endometrium.

If bleeding occurs before the end of the 10 day period, begin a 20 day estrogen-progestin cyclic regimen with PREMARIN (Conjugated Estrogens Tablets, U.S.P.), 2.5 to 7.5 mg daily in divided doses, for 20 days. During the last five days of estrogen therapy, give an oral progestin. If bleeding occurs before this regimen is concluded, therapy is discontinued and may be resumed on the fifth day of bleeding.

Female castration and primary ovarian failure—1.25 mg daily, cyclically. Adjust upward or downward according to response of the patient. For maintenance, adjust dosage to lowest level that will provide effective control.

Osteoporosis (to retard progression)—1.25 mg daily, cyclically.

3. *Given for a few days:* Prevention of postpartum breast engorgement—3.75 mg every four hours for five doses, or 1.25 mg every four hours for five days.

4. *Given chronically:* Inoperable progressing prostatic cancer—1.25 to 2.5 mg three times daily.

Inoperable progressing breast cancer in appropriately selected men and postmenopausal women—10 mg three times daily for a period of at least three months.

Patients with an intact uterus should be monitored for signs of endometrial cancer and appropriate measures taken to rule out malignancy in the event of persistent or recurring abnormal vaginal bleeding.

PREMARIN® Brand of Conjugated Estrogens, U.S.P. Vaginal Cream

Given cyclically for short-term use only. For treatment of atrophic vaginitis or kraurosis vulvae.

The lowest dose that will control symptoms should be chosen and medication should be discontinued as promptly as possible.

Administration should be cyclic (e.g., three weeks on and one week off).

Attempts to discontinue or taper medication should be made at three to six month intervals.

Usual dosage range: 2 to 4 g daily, intravaginally or topically, depending on the severity of the condition.

Treated patients with an intact uterus should be monitored closely for signs of endometrial cancer and appropriate diagnostic measures should be taken to rule out malignancy in the event of persistent or recurring abnormal vaginal bleeding.

HOW SUPPLIED: PREMARIN (Conjugated Estrogens Tablets, U.S.P.). No. 865—Each *purple* tablet contains 2.5 mg in bottles of 100 and 1,000. No. 866—Each *yellow* tablet contains 1.25 mg in bottles of 100 and 1,000. Also in Cycle Pack of 21 and in unit dose package of 100. No. B64—Each *white* tablet contains 0.9 mg in bottles of 100. Also in Cycle Pack of 21. No. 867—Each *maroon* tablet contains 0.625 mg in bottles of 100 and 1,000. Also in Cycle Pack of 21 and unit dose package of 100. No. B68—Each *green* tablet contains 0.3 mg in bottles of 100 and 1,000. The appearance of these tablets is a trademark of Ayerst Laboratories.

PREMARIN (Conjugated Estrogens, U.S.P.) Vaginal Cream No. B72. Each gram contains 0.625 mg Conjugated Estrogens, U.S.P. (Also contains cetyl esters wax, cetyl alcohol, white wax, glyceryl monostearate, propylene glycol monostearate, methyl stearate, phenylethyl alcohol, sodium lauryl sulfate, glycerin, and mineral oil.)

Combination package: Each contains Net Wt. 1½ oz. (42.5 g) tube with one calibrated plastic applicator.

Also Available—Refill package: Each contains Net Wt. 1½ oz. (42.5 g) tube. 4340R1/285

References: 1. Lindsay R, Hart DM, Clark DM: The minimum effective dose of estrogen for prevention of postmenopausal bone loss. *Obstet Gynecol* 1984;63:759-763. **2.** Katz WA: *Rheumatic Diseases. Diagnosis and Management.* Philadelphia, JB Lippincott Co, 1977, p 672. **3.** Reese WD: A better way to screen for osteoporosis. *Contemp Ob/Gyn* 1983,22(November):116-131. **4.** Judd HL: After the menopause. *Transition* 1983;1:19-30. **5.** Erlik Y, Tataryn IV, Meldrum DR, et al: Association of waking episodes with menopausal hot flushes. *JAMA* 19B1,245:1741-1744. **6.** Meldrum DR: The pathophysiology of postmenopausal symptoms. *Sem Reprod Endocrinol* 1983,1(February):11-17.

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(Continued from Page 771)

August 22-25—**Intermountain Dermatology Society.** Red Fish Lake Lodge, Idaho. Thursday-Sunday. 9½ hrs. Sponsor: University of Utah. Contact: C. David Hansen, MD, (801) 321-1100.

September 8-14—**Up-to-Date Cardiac Therapy.** Middle Fork of the Salmon River, Idaho White Water Rafting. Sunday-Saturday. 24 hrs. Cat. I. Sponsors: University of Arizona College of Medicine and Epic Medical Expeditions. Contact: Richard Paris, MD, PO Box 209, Sun Valley 83353. (208) 788-4995.

October 12-18—**Effective Diagnosis and Treatment of Infectious Diseases.** Salmon River, Idaho Sports Fishing. Saturday-Friday. 24 hrs. Cat I. Sponsors: University of Arizona College of Medicine and Epic Medical Expeditions. Contact: Richard Paris, MD, PO Box 209, Sun Valley 83353. (208) 788-4995.

MONTANA

October 3-5—**Montana Medical Association Annual Meeting.** Outlaw Inn, Kalispell. Thursday-Saturday. Contact: NNA, 2012 11th Ave., Ste. 12, Helena 59601. (406) 443-4000.

NEW MEXICO

Information, requests for accreditation and items to be listed should be sent to the chairman of the CME Committee, New Mexico Medical Society, 303 San Mateo NE, Suite 204, Albuquerque, NM 87108 at least two months in advance. For information on CME accreditation or on the CME requirements of the New Mexico Board of Medical Examiners, please write to the above address or call (505) 266-7868.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution for current details.

July 11-13—**General Surgical Update.** Albuquerque. Thursday-Saturday. Marriott Hotel. AMA Cat. I. Contact: Office of CME, UNM SOM, Albuquerque 87131. (505) 277-3942.

July 11-13—**Annual Meeting—New Mexico Ophthalmological Society.** Santa Fe. Thursday-Saturday. Hilton Inn. 8½ hrs. AMA Cat. I. Contact: John M. Mezoff, MD, 508 Cabezon Court, Gallup 87301.

July 15-18—**28th Annual Ruidoso Family Practice Seminar.** Mescalero. Monday-Thursday. Inn of the Mountain Gods. 20 hrs. AMA Cat. I and AAFP Prescribed Credit. Contact: NM Chapter, AAFP, PO Box 23070, Albuquerque 87192. (505) 298-5300.

OREGON

The following list of continuing medical offerings in the state of Oregon is compiled by the Oregon Medical Association's Council on Medical Education. If you wish to submit information regarding future postgraduate courses, please submit the information to James A. Kronenberg, Associate Executive Director, Oregon Medical Association, 5210 SW Corbett Ave., Portland, OR 97201, or phone (503) 226-1555.

MEDICAL GRAND ROUNDS

Douglas Community Hospital, 738 West Harvard Avenue, Roseburg 97470:

Every Monday, 12:30 p.m. Contact: Robert A. Driver, MD, Douglas Community Hospital, 738 West Harvard Avenue, Roseburg, OR 97470. (503) 673-6641.

Emanuel Hospital, 2801 N. Gantenbein Street, Portland 97227:

Every Friday, 8:00 a.m. to 9:00 a.m. **Medical Grand Rounds.** Contact: Philipa McClure, Emanuel Hospital, 2801 N. Gantenbein Street, Portland, OR 92227. (505) 280-3200.

Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland 97210:

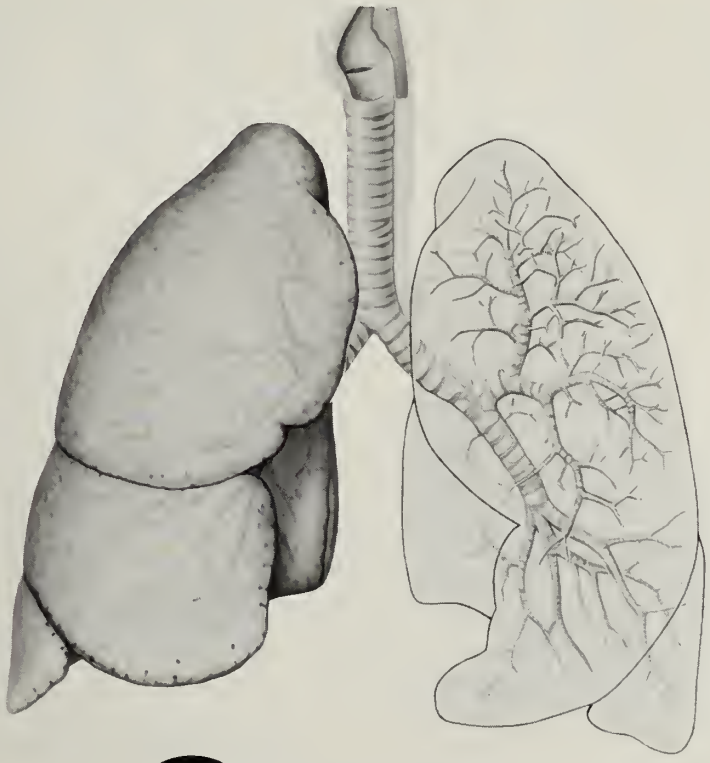
Every Wednesday, 8:00 a.m. to 9:00 a.m. **Medicine Grand Rounds.** Nursing Education Building, Room 110. Contact: Department of Medicine, Good Samaritan Hospital and Medical Center, 1015 NW 22nd Avenue, Portland, OR 97201. (503) 229-7454.

CONTACT INFORMATION

OHSU-CME—Contact: Division of Continuing Medical Education, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8700.

(Continued on Page 876)

Consider the causative organisms...



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cefaclor
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offers effectiveness against the major causes of bacterial bronchitis

H. influenzae, *H. influenzae*, *S. pneumoniae*, *S. pyogenes*
(ampicillin-susceptible) (ampicillin-resistant)

Brief Summary Consult the package literature for prescribing information

Indications and Usage: Ceclor* (cefaclor, Lilly) is indicated in the treatment of the following infections when caused by susceptible strains of the designated microorganisms

Lower respiratory infections, including pneumonia caused by *Streptococcus pneumoniae (Diplococcus pneumoniae), Haemophilus influenzae*, and *S. pyogenes* (group A beta-hemolytic streptococci)

Appropriate culture and susceptibility studies should be performed to determine susceptibility of the causative organism to Ceclor

Contraindication: Ceclor is contraindicated in patients with known allergy to the cephalosporin group of antibiotics

Warnings: IN PENICILLIN-SENSITIVE PATIENTS, CEPHALOSPORIN ANTIBIOTICS SHOULD BE ADMINISTERED CAUTIOUSLY THERE IS CLINICAL AND LABORATORY EVIDENCE OF PARTIAL CROSS-ALLERGENICITY OF THE PENICILLINS AND THE CEPHALOSPORINS, AND THERE ARE INSTANCES IN WHICH PATIENTS HAVE HAD REACTIONS, INCLUDING ANAPHYLAXIS, TO BOTH DRUG CLASSES

Antibiotics, including Ceclor, should be administered cautiously to any patient who has demonstrated some form of allergy, particularly to drugs

Pseudomembranous colitis has been reported with virtually all broad-spectrum antibiotics (including macrolides, semisynthetic penicillins, and cephalosporins); therefore, it is important to consider its diagnosis in patients who develop diarrhea in association with the use of antibiotics. Such colitis may range in severity from mild to life-threatening

Treatment with broad-spectrum antibiotics alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis

Mild cases of pseudomembranous colitis usually respond to drug discontinuance alone. In moderate to severe cases, management should include sigmoidoscopy, appropriate bacteriologic studies, and fluid, electrolyte, and protein supplementation. When the colitis does not improve after the drug has been discontinued, or when it is severe, oral vancomycin is the drug of choice for antibiotic-associated pseudomembranous colitis produced by *C. difficile*. Other causes of colitis should be ruled out

Precautions: *General Precautions* — If an allergic reaction to Ceclor* (cefaclor, Lilly) occurs, the drug should be discontinued, and, if necessary, the patient should be treated with appropriate agents, e.g., pressor amines, antihistamines, or corticosteroids

Prolonged use of Ceclor may result in the overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken

Positive direct Coombs' tests have been reported during treatment with the cephalosporin antibiotics. In hematologic studies or in transfusion cross-matching procedures when antiglobulin tests are performed on the minor side or in Coombs' testing of newborns whose mothers have received cephalosporin antibiotics before parturition, it should be recognized that a positive Coombs' test may be due to the drug

Ceclor should be administered with caution in the presence of markedly impaired renal function. Under such conditions, careful clinical observation and laboratory studies should be made because safe dosage may be lower than that usually recommended

As a result of administration of Ceclor, a false-positive reaction for glucose in the urine may occur. This has been observed with Benedict's and Fehling's solutions and also with Clinitest* tablets but not with Tes-Tape* (Glucose Enzymatic Test Strip, USP, Lilly).

Broad-spectrum antibiotics should be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis

Usage in Pregnancy — Pregnancy Category B — Reproduction studies have been performed in mice and rats at doses up to 12 times the human dose and in ferrets given three times the maximum human dose and have revealed no evidence of impaired fertility or harm to the fetus due to Ceclor* (cefaclor, Lilly). There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed

Nursing Mothers — Small amounts of Ceclor have been detected in mother's milk following administration of single 500-mg doses. Average levels were D 1-8, D 2-D, D 2-1, and D 1-6 mcg/ml at two, three, four, and five hours respectively. Trace amounts were detected at one hour. The effect on nursing infants is not known. Caution should be exercised when Ceclor is administered to a nursing woman.

Usage in Children — Safety and effectiveness of this product for use in infants less than one month of age have not been established

Adverse Reactions: Adverse effects considered related to therapy with Ceclor are uncommon and are listed below.

Gastrointestinal symptoms occur in about 2.5 percent of patients and include diarrhea (1 in 70).

Symptoms of pseudomembranous colitis may appear either during or after antibiotic treatment. Nausea and vomiting have been reported rarely.

Hypersensitivity reactions have been reported in about 1.5 percent of patients and include morbilliform eruptions (1 in 100). Pruritus, urticaria, and positive Coombs' tests each occur in less than 1 in 200 patients. Cases of serum-sickness-like reactions (erythema multiforme or the above skin manifestations accompanied by arthritis/arthralgia and, frequently, fever) have been reported. These reactions are apparently due to hypersensitivity and have usually occurred during or following a second course of therapy with Ceclor. Such reactions have been reported more frequently in children than in adults. Signs and symptoms usually occur a few days after initiation of therapy and subside within a few days after cessation of therapy. No serious sequelae have been reported. Antihistamines and corticosteroids appear to enhance resolution of the syndrome.

Cases of anaphylaxis have been reported, half of which have occurred in patients with a history of penicillin allergy.

Other effects considered related to therapy included eosinophilia (1 in 50 patients) and genital pruritus or vaginitis (less than 1 in 100 patients).

Causal Relationship Uncertain — Transitory abnormalities in clinical laboratory test results have been reported. Although they were of uncertain etiology, they are listed below to serve as alerting information for the physician.

Hepatic — Slight elevations in SGOT, SGPT, or alkaline phosphatase values (1 in 40).

Hematopoietic — Transient fluctuations in leukocyte count, predominantly lymphocytosis occurring in infants and young children (1 in 40).

Renal — Slight elevations in BUN or serum creatinine (less than 1 in 500) or abnormal urinalysis (less than 1 in 200).

[D617B2R]

Note: Ceclor* (cefaclor, Lilly) is contraindicated in patients with known allergy to the cephalosporins and should be given cautiously to penicillin-allergic patients.

Penicillin is the usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. See prescribing information.

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Additional information available to the profession on request from Eli Lilly and Company, Indianapolis, Indiana 46285

Eli Lilly Industries, Inc
Carolina, Puerto Rico 00630

(Continued from Page 874)

Providence Medical Center, 4805 NE Glisan, Portland 97213:

Every Wednesday, 8:00 a.m. **Medical Grand Rounds.** Contact: Richard Wernick, MD, Providence Medical Center, 4805 NE Glisan, Portland, OR 97213. (503) 230-6085.

Sacred Heart General Hospital, 1200 Alder Street, Eugene, OR 97440:

Every Tuesday, 8:00 a.m. to 9:00 a.m. **Medical Grand Rounds.** Hospital Auditorium. Contact: Medical Education Committee. PO Box 10905, Eugene, OR 97440.

Salem Hospital, 665 Winter Street SE, Salem 97301:

First and third Thursday of each month 7:15 a.m. to 8:15 a.m. **Medical Live Audit Conference.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter Street SE, Salem, OR 97301. (503) 370-5339.

Every Friday, 7:30 a.m. to 8:30 a.m. **Friday Grand Rounds.** Memorial Auditorium. Contact: Diane Eyerly, Salem Hospital, 665 Winter Street SE, Salem, OR 97301. (503) 370-5339.

St. Vincent Hospital & Medical Center, 9205 SW Barnes Road, Portland 97225:

First, third, fourth and fifth Wednesday of each month, 8:00 a.m. to 9:00 a.m. **Medical Grand Rounds.** Souther Auditorium. Contact: Bonnie Conger, Secretary to Dr Kenneth Melvin, St. Vincent Hospital & Medical Center, 9205 SW Barnes Road, Portland 97225. (503) 297-4411, Ext. 2230

Oregon Health Sciences University, Department of Psychiatry, Portland 97201:

Every Wednesday, 4:00 p.m. to 5:00 p.m. **Department of Psychiatry Grand Round Presentations.** Room 8B-60, University Hospital South, Oregon Health Sciences University. Contact: Dept. of Psychiatry, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8144.

Oregon Health Sciences University, Department of Medicine, Portland 97201:

Every Tuesday, 8:00 a.m. to 9:00 a.m. **Department of Medicine Grand Rounds.** U.H.S.-8B-60. Oregon Health Sciences University. Contact: Dept. of Medicine, Oregon Health Sciences University, Portland, OR 97201. (503) 225-8607.

FAMILY PRACTICE GRAND ROUNDS

Every Wednesday, 11:00 a.m. to 12:00 Noon. **Family Practice Grand Rounds.** Family Practice Center, Oregon Health Sciences University, Portland. Contact: William A. Fisher, MD, Oregon Health Sciences University, Department of Family Practice, Portland, OR 97201. (503) 225-7590.

OF INTEREST TO ALL PHYSICIANS

June 28—**Osteoporosis Conference.** Portland. Friday. Red Lion Lloyd Center. Contact: OHSU-CME.

July 7-10—**Plastic Surgery for the Primary Care Physician.** Sunriver. Sunday-Wednesday. Sunriver Resort. Contact: OHSU-CME.

September 6-7—**Ashland Conference: Infectious Disease.** Ashland. Friday-Saturday. Ashland Hills Inn. Contact: OHSU-CME.

October 4-5—**Fifth Annual Toxicology Conference.** Portland. Friday-Saturday. Marriott Hotel. Contact: OHSU-CME.

UTAH

This listing of continuing medical education courses in Utah is compiled and edited by the CME office of the Utah State Medical Association. All courses listed have been certified by CME accredited institutions as meeting the criteria for Category 1 of the Physician's Recognition Award of the American Medical Association. They also must meet the definition of Utah Approved CME Credit for the purpose of medical license reregistration in Utah. Accredited institutions wishing to list AMA Category 1/Utah Approved CME courses here should send information at least two months in advance to the Office of Continuing Medical Education, 540 East Fifth South, Salt Lake City, Utah 84102; or phone (801) 355-5290. For information on CME accreditation or on the CME requirements of the Utah Physicians' Licensing Board, please write the CME office at the above address.

NOTE: Course information in the following listing is subject to change on occasion. Check with the sponsoring institution or the CME office for current details.

MEDICAL GRAND ROUNDS

Each Wednesday—8:00-9:00 a.m. Alternating between University of Utah Medical Center and VA Medical Center, Salt Lake City. Contact: William D. Odell, MD, PhD, Professor and Chairman, Dept. of Internal Medicine, Univ. of Utah, (801) 581-7606.

(Continued on Page 878)

PHYSICIANS

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(Continued from Page 876)

June 16-21—**Thirty-fourth Annual Session, School on Alcoholism/Drug Dependencies** (Sponsor: University of Utah). Sunday-Friday. University Medical Center-Wintrobe Building. 26 hrs. Contact: James Swenson, MD, (801) 533-5799.

July 14-19—**Summer Update in Clinical Microbiology and Immunology** (Sponsor: University of Utah). Sunday-Friday. Jackson Hole, American Snow King. 23 hrs. Contact: John Matsen, MD, (801) 581-7480.

August 5-7—**Seminars in Ultrasound, CT, MR** (Sponsor: University of Utah). Monday-Wednesday. Hyannis, Massachusetts. 13.5 hrs. Contact: William Zwiebel, MD, (801) 581-2800.

August 22-25—**Intermountain Dermatology Society** (Sponsor: University of Utah). Thursday-Sunday. Red Fish Lake Lodge, Idaho. 9.5 hrs. Contact: C. David Hansen, MD, (801) 321-1100.

SPONSORS OF COURSES—ABBREVIATIONS

AF: Arthritis Foundation, 1174 East 2700 South, Salt Lake City 84117. (801) 466-9389.

CH: Castleview Hospital (formerly Carbon Hospital), RFD 2, Box 46, Price, UT 84501. (801) 637-4800.

CWH: Cottonwood Hospital, 5770 South 300 East, Salt Lake City 84101. (801) 262-3461.

FHP: Family Health Program/Utah, 323 South Sixth East, Salt Lake City 84102. (801) 335-1234. Contact: Kay Schultz for course information.

HAFB: Hill Air Force Hospital, Hill Air Force Base 84406. (801) 777-1262.

HCH: Holy Cross Hospital, 1045 East First South, Salt Lake City 84102. (801) 350-4744.

LDSH: Latter-Day Saints Hospital, 325 8th Avenue, Salt Lake City 84143, (801) 350-1100.

MDH: McKay-Dee Hospital Center, 3939 Harrison Blvd., Ogden 84409. (801) 399-4141.

OEH: Rocky Mountain Center for Occupational and Environmental Health, 50 North Medical Drive, Salt Lake City 84132. (801) 581-8719.

OSS: Ogden Surgical Society, PO Box 9311, Ogden 84409.

PCMC: Primary Children's Medical Center, 320 12th Ave., Salt Lake City 84103. (801) 363-1221.

SHCC: Shriners Hospital for Crippled Children, Intermountain Unit, Fairfax Ave. at Virginia St., Salt Lake City 84103. (801) 532-5307.

SLSC: Salt Lake Surgical Center, 617 East 3900 South, Salt Lake City 84117. (801) 261-3141.

UAFP: Utah Academy of Family Physicians, 1146 Westminster Ave., Salt Lake City 84105. (801) 466-9478.

UUMC: University of Utah Medical Center, 50 North Medical Drive, Salt Lake City 84132. (801) 581-2258.

USMA: Utah State Medical Association, 540 East Fifth South, Salt Lake City 84102. (801) 355-7477.

UVH: Utah Valley Hospital, 1034 North Fifth West, Provo 84601. (801) 373-7850.

VAMC: Veterans Administration Medical Center, 500 Foothill Drive, Salt Lake City 84148. (801) 582-1565.

November 8-9—**Advanced Trauma Life Support** (Sponsor: University of Utah/Utah Department of Health). Friday-Saturday. Quality Inn, Salt Lake City. 16 hrs. Contact: Kim Tanner, (801) 533-6608.

WASHINGTON

This listing of continuing medical education programs in Washington state is compiled by the Washington State Medical Association. To list Category 1 programs here please send information at least two months in advance to Continuing Medical Education, Washington State Medical Association, 2033 Sixth Avenue, Suite 900, Seattle, WA 98121; or phone (206) 623-4801.

Brochures and Registration Forms are available from the contact person or organization listed at the end of each course or in the list of course sponsors and contact information.

June 15—**Contemporary Thoracic Imaging.** Seattle. Saturday. U/W South Campus Center. Contact: U/W.

June 18—**Small Computers in Medicine.** Seattle. Tuesday. Ballard Hospital. Contact: U/W.

June 18-20—**Financial Planning for Physicians.** Victoria, BC. Tuesday-Thursday. Empress Hotel. Contact: U/W.

June 21—**Riverton Hospital Lectures.** Seattle. Friday. Riverton Hospital. Contact: U/W.

June 21-22—**Nutrition of Hospitalized Patient.** Vancouver, BC. Friday-Saturday. Contact: U/W.

June 25—**What's New in Antibiotics.** Auburn. Tuesday. Auburn General Hospital. Contact: U/W.

COURSE SPONSORS AND CONTACT INFORMATION

CME HARBORVIEW—Contact: Gayle Splater, Cytology Continuing Education, Dept. of Pathology, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104. (206) 223-5953.

CME PIERCE COUNTY—Contact: Mrs Maxine Bailey, Executive Director, College of Medical Education, 705 South Ninth, No. 203, Tacoma, WA 98405. (206) 627-7137.

U/W (UNIVERSITY OF WASHINGTON)—Contact: U/W School of Medicine, Div. of CME, SC-50, Seattle, WA 98195. (206) 543-1050.

VMMC (VIRGINIA MASON MEDICAL CENTER)—Contact: Linda Orgel, Division of Continuing Medical Education, Virginia Mason Medical Center, PO Box 900, Seattle, WA 98111. (206) 223-6898.

(Continued on Page 887)

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In view of *The Copyright Revision Act of 1976,* transmittal letters should contain the following language: "In consideration for reviewing and editing my submission, the author(s) undersigned hereby transfers, assigns or otherwise conveys all copyright ownership to THE WESTERN JOURNAL OF MEDICINE in the event that such work is published by the journal." This statement should be signed by *all* the authors.

Authors are urged to seek clarity and succinctness in all manuscripts regardless of subject matter or format and to give close attention to syntax, grammar and spelling.

Clinical Investigation Section

Articles that authors wish to have considered for the Clinical Investigation section should be so designated in the transmittal letter. The type of articles appropriate for this section are those that describe experimental work in humans that extensively and prospectively examines scientific hypotheses relating to disease. An article describing a single case report will not normally be considered appropriate for this section.

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The original manuscript and *two* copies should be submitted on heavy bond paper (8½ by 11 inches, *not* erasable), typed *double-spaced throughout* (including legends, tables and references) on one side of the paper, with 1½-inch margins. Ordinarily, articles should not exceed 3,000 words (less than 15 text pages, typed double-spaced). Under exceptional circumstances only will articles longer than 4,000 words be published. Pages should be numbered consecutively, beginning with the title page.

Style

Abbreviations. Use of abbreviations should be minimized. If they are necessary, abbreviations should be spelled out at first mention, with the abbreviation itself immediately following in parentheses.

Weights and measures. All measurements should be given in metric units. English equivalents should be given parenthetically if the measurements were originally done in English units.

Temperatures. Temperature readings should be given first in Celsius, followed by the Fahrenheit equivalent in parentheses.

Drug names. If the trade name of a drug is used, the generic name should be given first, followed by the trade name in parentheses. Trade names are capitalized, generic names are not.

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Titles are best when brief and concise. The title page should include the full name of the author(s), with degrees, academic or professional titles, complete addresses and any institutional or other affiliations. The complete name and address of the person who will handle reprint requests also should appear on this page.

Abstract

The abstract (approximately 150 words) should be a short summary, saying in brief what is said at length in the body of the article—rather than such and such "is discussed," "is presented" or "was investigated."

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Each table should be typed on a separate sheet of paper, be numbered consecutively in Arabic numerals, have a brief descriptive title and have its position indicated in the text.

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Three sets of clear, unmounted black and white glossy prints of figures should be submitted (preferably 5 by 7 inches, but no larger than 8½ by 11 inches). For line drawings, original artwork or glossy prints are acceptable. Illustrations should be numbered consecutively in Arabic numerals and their position indicated in the text. Figure number, first author's name and top of the photo should be shown on the reverse side of each illustration. Recognizable photographs of patients are to be masked and written permission for publication obtained from the patients.

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References should be limited to those cited in the text. They must be typed double-spaced and numbered consecutively as they appear in the manuscript. (See examples below for style.) Abbreviations of journal titles should conform to those used in *Index Medicus.*

Journal Articles

Note handling of multiple authorship. If more than three authors are listed as contributors, use "et al" to designate those names after the first three. Also note capitalization, punctuation, mention of inclusive page numbers and year of publication. Separate the subtitle from the title by either a dash or a colon. Use colon *only* if it appears in the original citation.

1. Jones JS, Anderson HW, Johnson DW, et al: The athletic heart revisited—Sudden death of a 28-year-old athlete. JAMA 1978; 292:444-456

2. Graybill JR, Alford RH, Smith RG, et al: Cell-mediated immunity in cryptococcosis: A brief review. Cell Immunol 1978; 7:76-79

Books

Note handling of "edition," "editor(s)," and "volume," as well as appropriate sequence of reference information and capitalization of chapters and titles.

3. Berne EJ, Smith TL: Role playing in therapy, chap 2, Principles of Group Therapy. New York, Oxford University Press, 1966, pp 35-51 *(author of chapter same as author of book)*

4. Munsung JM: The role of drugs, chap 2, *In* Brest AN, Mayer JH (Eds): Hypertension—Vol 2, Therapy, 2nd Ed. Springfield, Ill, Charles C Thomas, 1961, pp 456-479 *(author of chapter different from authors of book)*

Pamphlets, Monographs or Books With No Given Author

5. AMA Department of Drugs: AMA Drug Evaluation, 3rd Ed. Littleton, Mass, Publishing Sciences Group, 1977 *(corporate author)*

6. Compilation of Standard Definitions, 3rd Ed. Philadelphia, American Society for Testing and Materials, 1976 *(no given author; give name and place of publisher)*

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Any article accepted for publication should include the name of the journal (appropriately abbreviated) in which it will appear, and the phrase "in press" or "accepted for publication" in place of the date of publication.

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Brief manuscripts commenting on articles that have appeared in the journal, containing information of interest to physicians or discussing issues of the day will be considered for publication. Very short reports of cases, clinical experience, clinical studies, adverse effects and the like also will be considered. Items for the Correspondence section should not exceed 600 words and should have no more than five bibliographic references and one figure or table.

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References:
1. Strauss WE, McIntyre KM, Parisi AF, et al: Safety and efficacy of diltiazem hydrochloride for the treatment of stable angina pectoris: Report of a cooperative clinical trial. Am J Cardiol 49:560-566, 1982.
2. Pool PE, Seagren SC, Bonanno JA, et al: The treatment of exercise-inducible chronic stable angina with diltiazem: Effect on treadmill exercise. Chest 78 (July suppl):234-238, 1980.

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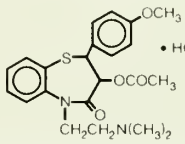
DESCRIPTION

CARDIZEM® (diltiazem hydrochloride) is a calcium ion influx inhibitor (slow channel blocker or calcium antagonist). Chemically, diltiazem hydrochloride is 1,5-Benzothiazepin-4(5H)one,3-(acetyloxy) -5-[2-(dimethylamino)ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-, monohydrochloride,(+)-cis-. The chemical structure is:



Diltiazem hydrochloride is a white to off-white crystalline powder with a bitter taste. It is soluble in water, methanol, and chloroform. It has a molecular weight of 450.98. Each tablet of CARDIZEM contains either 30 mg or 60 mg diltiazem hydrochloride for oral administration.

CLINICAL PHARMACOLOGY

The therapeutic benefits achieved with CARDIZEM are believed to be related to its ability to inhibit the influx of calcium ions during membrane depolarization of cardiac and vascular smooth muscle.

Mechanisms of Action. Although precise mechanisms of its antianginal actions are still being delineated, CARDIZEM is believed to act in the following ways:

1. Angina Due to Coronary Artery Spasm: CARDIZEM has been shown to be a potent dilator of coronary arteries both epicardial and subendocardial. Spontaneous and ergonovine-induced coronary artery spasm are inhibited by CARDIZEM.
2. Exertional Angina: CARDIZEM has been shown to produce increases in exercise tolerance, probably due to its ability to reduce myocardial oxygen demand. This is accomplished via reductions in heart rate and systemic blood pressure at submaximal and maximal exercise work loads.

In animal models, diltiazem interferes with the slow inward (depolarizing) current in excitable tissue. It causes excitation-contraction uncoupling in various myocardial tissues without changes in the configuration of the action potential. Diltiazem produces relaxation of coronary vascular smooth muscle and dilation of both large and small coronary arteries at drug levels which cause little or no negative inotropic effect. The resultant increases in coronary blood flow (epicardial and subendocardial) occur in ischemic and nonischemic models and are accompanied by dose-dependent decreases in systemic blood pressure and decreases in peripheral resistance.

Hemodynamic and Electrophysiologic Effects. Like other calcium antagonists, diltiazem decreases sinoatrial and atrioventricular conduction in isolated tissues and has a negative inotropic effect in isolated preparations. In the intact animal, prolongation of the AH interval can be seen at higher doses.

In man, diltiazem prevents spontaneous and ergonovine-provoked coronary artery spasm. It causes a decrease in peripheral vascular resistance and a modest fall in blood pressure and, in exercise tolerance studies in patients with ischemic heart disease, reduces the heart rate-blood pressure product for any given work load. Studies to date, primarily in patients with good ventricular function, have not revealed evidence of a negative inotropic effect; cardiac output, ejection fraction, and left ventricular end diastolic pressure have not been affected. There are as yet few data on the interaction of diltiazem and beta-blockers. Resting heart rate is usually unchanged or slightly reduced by diltiazem.

Intravenous diltiazem in doses of 20 mg prolongs AH conduction time and AV node functional and effective refractory periods approximately 20%. In a study involving single oral doses of 300 mg of CARDIZEM in six normal volunteers, the average maximum PR prolongation was 14% with no instances of greater than first-degree AV block. Diltiazem-associated prolongation of the AH interval is not more pronounced in patients with first-degree heart block. In patients with sick sinus syndrome, diltiazem significantly prolongs sinus cycle length (up to 50% in some cases).

Chronic oral administration of CARDIZEM in doses of up to 240 mg/day has resulted in small increases in PR interval, but has not usually produced abnormal prolongation. There were, however, three instances of second-degree AV block and one instance of third-degree AV block in a group of 959 chronically treated patients.

Pharmacokinetics and Metabolism. Diltiazem is absorbed from the tablet formulation to about 80% of a reference capsule and is subject to an extensive first-pass effect, giving an absolute bioavailability (compared to intravenous dosing) of about 40%. CARDIZEM undergoes extensive hepatic metabolism in which 2% to 4% of the unchanged drug appears in the urine. In vitro binding studies show CARDIZEM is 70% to 80% bound to plasma proteins. Competitive ligand binding studies have also shown CARDIZEM binding is not altered by therapeutic concentrations of digoxin, hydrochlorothiazide, phenylbutazone, propranolol, salicylic acid, or warfarin. Single oral doses of 30 to 120 mg of CARDIZEM result in detectable plasma levels within 30 to 60 minutes and peak plasma levels two to three hours after drug administration. The plasma elimination half-life following single or multiple drug administration is approximately 3.5 hours. Desacetyl diltiazem is also present in the plasma at levels of 10% to 20% of the parent drug and is 25% to 50% as potent a coronary vasodilator as diltiazem. Therapeutic blood levels of CARDIZEM appear to be in the range of 50 to 200 ng/ml. There is a departure from dose-linearity when single doses above 60 mg are given; a 120-mg dose gave blood levels three times that of the 60-mg dose. There is no information about the effect of renal or hepatic impairment on excretion or metabolism of diltiazem.

INDICATIONS AND USAGE

1. **Angina Pectoris Due to Coronary Artery Spasm.** CARDIZEM is indicated in the treatment of angina pectoris due to coronary artery spasm. CARDIZEM has been shown effective in the treatment of spontaneous coronary artery spasm presenting as Prinzmetal's variant angina (resting angina with ST-segment elevation occurring during attacks).
2. **Chronic Stable Angina (Classic Effort-Associated Angina).** CARDIZEM is indicated in the management of chronic stable angina. CARDIZEM has been effective in controlled trials in reducing angina frequency and increasing exercise tolerance.

There are no controlled studies of the effectiveness of the concomitant use of diltiazem and beta-blockers or of the safety of this combination in patients with impaired ventricular function or conduction abnormalities.

CONTRAINDICATIONS

CARDIZEM is contraindicated in (1) patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker, (2) patients with second- or third-degree AV block except in the presence of a functioning ventricular pacemaker, and (3) patients with hypotension (less than 90 mm Hg systolic).

WARNINGS

1. **Cardiac Conduction.** CARDIZEM prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (six of 1243 patients for 0.48%). Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction. A patient with Prinzmetal's angina developed periods of asystole (2 to 5 seconds) after a single dose of 60 mg of diltiazem.
2. **Congestive Heart Failure.** Although diltiazem has a negative inotropic effect in isolated animal tissue preparations, hemodynamic studies in humans with normal ventricular function have not shown a reduction in cardiac index nor consistent negative effects on contractility (dp/dt). Experience with the use of CARDIZEM alone or in combination with beta-blockers in patients with impaired ventricular function is very limited. Caution should be exercised when using the drug in such patients.
3. **Hypotension.** Decreases in blood pressure associated with CARDIZEM therapy may occasionally result in symptomatic hypotension.
4. **Acute Hepatic Injury.** In rare instances, patients receiving CARDIZEM have exhibited reversible acute hepatic injury as evidenced by moderate to extreme elevations of liver enzymes. (See PRECAUTIONS and ADVERSE REACTIONS.)

PRECAUTIONS

General. CARDIZEM (diltiazem hydrochloride) is extensively metabolized by the liver and excreted by the kidneys and in bile. As with any new drug given over prolonged periods, laboratory parameters should be monitored at regular intervals. The drug should be used with caution in patients with impaired renal or hepatic function. In subacute and chronic dog and rat studies designed to produce toxicity, high doses of diltiazem were associated with hepatic damage. In special subacute hepatic studies, oral doses of 125 mg/kg and higher in rats were associated with histological changes in the liver which were reversible when the drug was discontinued. In dogs, doses of 20 mg/kg were also associated with hepatic changes; however, these changes were reversible with continued dosing.

Drug Interaction. Pharmacologic studies indicate that there may be additive effects in prolonging AV conduction when using beta-blockers or digitalis concomitantly with CARDIZEM. (See WARNINGS).

Controlled and uncontrolled domestic studies suggest that concomitant use of CARDIZEM and beta-blockers or digitalis is usually well tolerated. Available data are not sufficient, however, to predict the effects of concomitant treatment, particularly in patients with left ventricular dysfunction or cardiac conduction abnormalities. In healthy volunteers, diltiazem has been shown to increase serum digoxin levels up to 20%.

Carcinogenesis, Mutagenesis, Impairment of Fertility. A 24-month study in rats and a 21-month study in mice showed no evidence of carcinogenicity. There was also no mutagenic response in in vitro bacterial tests. No intrinsic effect on fertility was observed in rats.

Pregnancy. Category C. Reproduction studies have been conducted in mice, rats, and rabbits. Administration of doses ranging from five to ten times greater (on a mg/kg basis) than the daily recommended therapeutic dose has resulted in embryo and fetal lethality. These doses, in some studies, have been reported to cause skeletal abnormalities. In the perinatal/postnatal studies, there was some reduction in early individual pup weights and survival rates. There was an increased incidence of stillbirths at doses of 20 times the human dose or greater.

There are no well-controlled studies in pregnant women; therefore, use CARDIZEM in pregnant women only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when CARDIZEM is administered to a nursing woman if the drug's benefits are thought to outweigh its potential risks in this situation.

Pediatric Use. Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Serious adverse reactions have been rare in studies carried out to date, but it should be recognized that patients with impaired ventricular function and cardiac conduction abnormalities have usually been excluded.

In domestic placebo-controlled trials, the incidence of adverse reactions reported during CARDIZEM therapy was not greater than that reported during placebo therapy.

The following represent occurrences observed in clinical studies which can be at least reasonably associated with the pharmacology of calcium influx inhibition. In many cases, the relationship to CARDIZEM has not been established. The most common occurrences, as well as their frequency of presentation, are: edema (2.4%), headache (2.1%), nausea (1.9%), dizziness (1.5%), rash (1.3%), asthenia (1.2%), AV block (1.1%). In addition, the following events were reported infrequently (less than 1%) with the order of presentation corresponding to the relative frequency of occurrence.

Cardiovascular:	Flushing, arrhythmia, hypotension, bradycardia, palpitations, congestive heart failure, syncope.
Nervous System:	Paresthesia, nervousness, somnolence, tremor, insomnia, hallucinations, and amnesia.
Gastrointestinal:	Constipation, dyspepsia, diarrhea, vomiting, mild elevations of alkaline phosphatase, SGOT, SGPT, and LDH.
Dermatologic:	Pruritus, petechiae, urticaria, photosensitivity.
Other:	Polyuria, nocturia.

The following additional experiences have been noted:

A patient with Prinzmetal's angina experiencing episodes of vasospastic angina developed periods of transient asymptomatic asystole approximately five hours after receiving a single 60-mg dose of CARDIZEM.

The following postmarketing events have been reported infrequently in patients receiving CARDIZEM: erythema multiforme; leukopenia; and extreme elevations of alkaline phosphatase, SGOT, SGPT, LDH, and CPK. However, a definitive cause and effect between these events and CARDIZEM therapy is yet to be established.

OVERDOSAGE OR EXAGGERATED RESPONSE

Overdosage experience with oral diltiazem has been limited. Single oral doses of 300 mg of CARDIZEM have been well tolerated by healthy volunteers. In the event of overdosage or exaggerated response, appropriate supportive measures should be employed in addition to gastric lavage. The following measures may be considered:

Bradycardia	Administer atropine (0.60 to 1.0 mg). If there is no response to vagal blockade, administer isoproterenol cautiously.
High-Degree AV Block	Treat as for bradycardia above. Fixed high-degree AV block should be treated with cardiac pacing.
Cardiac Failure	Administer inotropic agents (isoproterenol, dopamine, or dobutamine) and diuretics.
Hypotension	Vasopressors (eg, dopamine or levarterenol bitartrate).

Actual treatment and dosage should depend on the severity of the clinical situation and the judgment and experience of the treating physician.

The oral LD_{50}'s in mice and rats range from 415 to 740 mg/kg and from 560 to 810 mg/kg, respectively. The intravenous LD_{50}'s in these species were 60 and 38 mg/kg, respectively. The oral LD_{50} in dogs is considered to be in excess of 50 mg/kg, while lethality was seen in monkeys at 360 mg/kg. The toxic dose in man is not known, but blood levels in excess of 800 ng/ml have not been associated with toxicity.

DOSAGE AND ADMINISTRATION

Exertional Angina Pectoris Due to Atherosclerotic Coronary Artery Disease or Angina Pectoris at Rest Due to Coronary Artery Spasm. Dosage must be adjusted to each patient's needs. Starting with 30 mg four times daily, before meals and at bedtime, dosage should be increased gradually (given in divided doses three or four times daily) at one- to two-day intervals until optimum response is obtained. Although individual patients may respond to any dosage level, the average optimum dosage range appears to be 180 to 240 mg/day. There are no available data concerning dosage requirements in patients with impaired renal or hepatic function. If the drug must be used in such patients, titration should be carried out with particular caution.

Concomitant Use With Other Antianginal Agents:

1. **Sublingual NTG** may be taken as required to abort acute anginal attacks during CARDIZEM therapy.
2. **Prophylactic Nitrate Therapy**—CARDIZEM may be safely coadministered with short- and long-acting nitrates, but there have been no controlled studies to evaluate the antianginal effectiveness of this combination.
3. **Beta-blockers.** (See WARNINGS and PRECAUTIONS.)

HOW SUPPLIED

Cardizem 30-mg tablets are supplied in bottles of 100 (NDC 0088-1771-47) and in Unit Dose Identification Paks of 100 (NDC 0088-1771-49). Each green tablet is engraved with MARION on one side and 1771 engraved on the other. CARDIZEM 60-mg scored tablets are supplied in bottles of 100 (NDC 0088-1772-47) and in Unit Dose Identification Paks of 100 (NDC 0088-1772-49). Each yellow tablet is engraved with MARION on one side and 1772 on the other.

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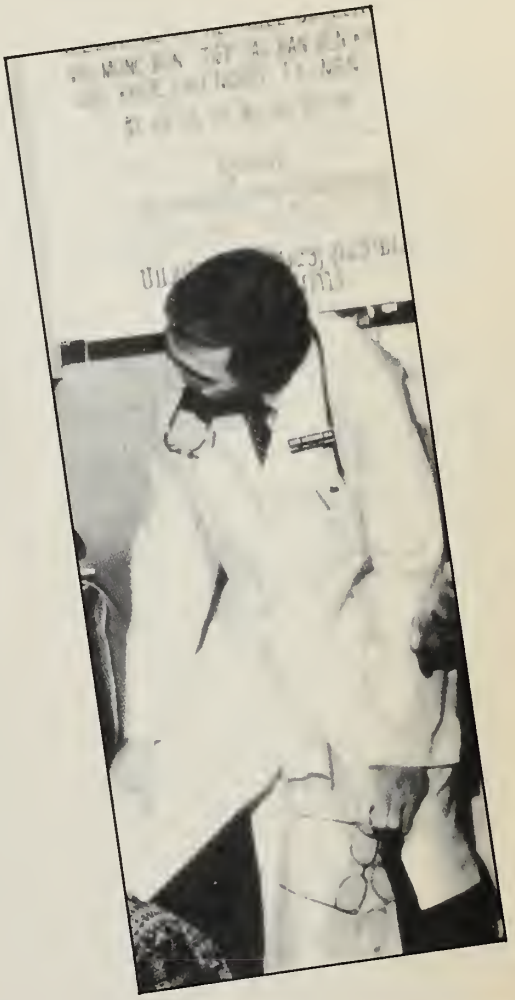

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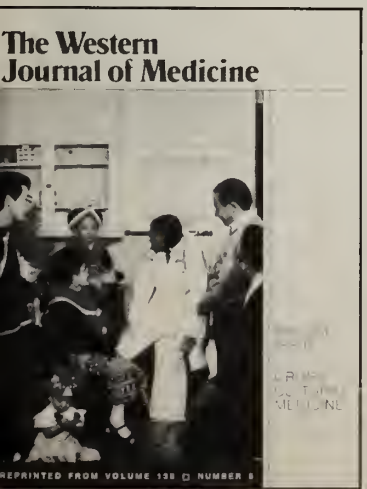

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Prestigious HMO is seeking experienced specialists and general practitioners for our facilities in Los Angeles and Orange Counties. Located in close proximity to major teaching centers, we offer the opportunity for continued professional development and rewarding clinical practice. Excellent compensation and benefits including paid malpractice, life, disability, medical and dental coverage, paid vacations, sick leave, educational leave and retirement plan. Please send CV to: Director/Physician Recruitment, CIGNA Healthplans of California, 700 North Brand Blvd., Suite 500-49, Glendale, CA 91203.

SOUTH DAKOTA: Expanding physician-owned emergency group has opening for full-time career-oriented Emergency Physicians in South Dakota. Excellent benefits including malpractice, disability, health insurance, profit sharing, etc. Flexible work schedules, excellent working and living conditions. Contact Donald Kougl, MD, (307) 632-1436 or send CV to EMP, P.C., PO Box 805, Cheyenne, WY 82003.

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WCH Westworld Community Healthcare, Inc.

BEDROOM COMMUNITY OF LOS ANGELES—ENDOCRINOLOGIST/INTERNIST for private practice with two Board certified Internists. For details, contact E. Gusman, 2800 Veterans Blvd., Suite 170, Metairie, LA 70002 or call toll-free 1 (800) 535-7698. If within Louisiana, call collect (504) 835-0991.

FAMILY PRACTICE PHYSICIAN to join 15 physician multispecialty group located in Southern Idaho. Send résumé to Business Administrator, Box 1233, Twin Falls, ID 83301.

PHYSICIANS WANTED

INSTITUTION PHYSICIAN needed to staff the Wyoming State Training School at Lander, Wyoming. We have 420 mentally retarded residents with a 30 bed Health Care Center with a staff of four physicians. Attractive salary and fringe benefits. No overhead. Pleasant surrounding area including an excellent medical group in Lander. If interested, please contact the Personnel Manager, Wyoming State Training School, 8204 State Highway 789, Lander, WY 82520. An Equal Opportunity Employer.

FAMILY PRACTICE opportunity in eastern New Mexico. Join two physicians in private practice situation with an established patient population. Must do OB. No buy-in; just share expenses and call. Family community with stable economy. Contact Bill Norris, Southwest Community Health Services, PO Box 26666, Albuquerque, NM 87125-6666, or call 1 (800) 545-4030, ext. 3050.

EUGENE, OREGON: FP/GP to join staff in salaried position with clinic providing outpatient and hospital care primarily to low income population. Half-time to start, flexible scheduling. Contact: Michael Weinstein, MD, 323 East 12th Ave, Eugene, OR 97401; (503) 484-4800.

ANESTHESIOLOGIST WANTED. Board certified or eligible. Competitive salary, leading to partnership in small western town. 120 bed hospital. Good schools available, outdoor recreation nearby. Position available June 1. Send CV to: Box 6477, Western Journal of Medicine, 44 Gough St., San Francisco, CA 94103.

WASHINGTON: Expanding physician-owned emergency group has opening for full-time career-oriented Emergency Physicians in south central Washington. Excellent benefits including malpractice, disability, health insurance, profit sharing, etc. Flexible work schedules, excellent working and living conditions. Contact Donald Kougl, MD, (307) 632-1436 or send CV to EMP, P.C., PO Box 805, Cheyenne, WY 82003.

INTERNIST or Internal Medicine subspecialist to share medical suite and overhead expenses with recently-established Rheumatologist in excellent Modesto, California, location. Dr Rex Adams, PO Box 5375, Modesto, CA 95352-5375. No phone calls.

ASSOCIATE MEDICAL COORDINATOR—The California Department of Food and Agriculture has an immediate opportunity for a physician with graduate training in pharmacology/toxicology and experience in evaluating potential chemical intoxications to provide medical consultation to agencies and physicians dealing with pesticide chemicals in California. Evaluate data submitted to support registration applications for pesticides and make recommendations on regulations necessary to protect the health of pesticide workers and the public. Send résumé to: Department of Food and Agriculture, 1220 N St., Room 126, Sacramento, CA 95814, by June 14, 1985. Civil Service Interview required. Position located in Sacramento.

ACADEMIC GENERAL INTERNISTS, CARDIOLOGIST, AND ENDOCRINOLOGIST, DO—Wanted for full-time faculty positions. Must be Board admissible or certified, interested in teaching medical students and house staff. Good balance between clinical practice and teaching with research opportunities available. Assistant Professor level with excellent guaranteed salary and benefits. Send CV to Victor H. Kaylarian, DO, Department of Medicine, University of Osteopathic Medicine and Health Sciences, 3200 Grand Ave., Des Moines, IA 50312. All inquiries confidential.

PEDIATRICIAN FOR GENERAL PEDS AND NEWBORN. Energetic/young/good future for building up and expanding present practice. Los Angeles, Burbank. CV to 2625 West Alameda, Burbank, CA 91505, A. Resnik; (818) 843-6203.

(Continued on Page 886)

The Western Journal of Medicine

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(Continued from Page 884)

PHYSICIANS WANTED

INTERNAL MEDICINE

Excellent opportunity with California's established leading provider of executive fitness/industrial care, for Internist (Board certified eligible). IMMEDIATE FULL-TIME/PART-TIME Opening. Salary guaranteed plus production bonus. Malpractice and fringe benefits. Write: Personnel, Urgent Care Centers of America, Inc. 2737 Walsh Ave., Santa Clara, CA 95051; (408) 727-1900; EOE.

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Immediate full- of part-time opening with California's leading provider of industrial/private care. Orthopedist and neurologist needed for consultation, out-patient minor trauma. Industrial/Urgent Care Clinic. No nights, weekends, salary guarantee plus high incentive bonus. Malpractice and fringe benefits. Write: Personnel, Urgent Care Centers of America, Inc. 2737 Walsh Ave., Santa Clara, CA 95051; (408) 727-1900; EOE.

KETCHUM, SUN VALLEY, IDAHO: Internist, Surgeon, Pediatrician, Orthopedist in multispecialty, expanding, well-equipped clinic. Income moderate; quality of life highest. Dr Bryan Stone, PO Box 2198, Ketchum, ID 83340; (208) 726-9361.

OREGON: General Surgeon sought for 8 physician multispecialty group. Excellent opportunity. Beautiful rural community, 38 miles from Portland. Send CV to Administrator, 420 East 5th Street, McMinnville, OR 97128; (503) 472-6161.

HAYWARD, CALIFORNIA 20 man Bay Area multispecialty group with 4 pediatricians seeking Board certified or eligible Pediatrician to replace retired physician, May 1985. Group active in HMO's and satellite office. Contact: Donald L. Lass, Administrator, Hayward Medical Group, 27212 Calaroga Ave., Hayward, CA 94545; (415) 785-5000.

TWO BOARD CERTIFIED FAMILY PHYSICIANS NEEDED to join well established, busy practice in progressive community of 7,000 in Sierras, north of Sacramento. Broad Family Practice with OB and active hospital practice in 34 bed JCAH accredited hospital adjacent to office. Contact: Michael Gabe, MD, 1045 Bucks Lake Rd., Quincy, CA 95971; (916) 283-0650.

COMMUNITY HEALTH CENTER IN SAN FRANCISCO BAY AREA seeks to fill the following positions. Full time Medical Director for Administrator/Clinic responsibilities. Physician Internist part-time (53%). Family Practice Physician (60%). Requirements include Board eligible/certified, bilingual ability (Spanish/English). Salary negotiable. Send CV with all inquiries to: La Clinica De La Raza, 1515 Fruitvale Ave., Oakland, CA 94601, Attention Personnel; (415) 534-0078.

CALIFORNIA—Join a partnership of established physicians providing urgent and ambulatory care in both northern and southern California. Physicians earn a guaranteed minimum with a strong incentive package and have the opportunity to quickly become partners. Our attractive centers are rapidly growing! Please indicate your geographic preference (Los Angeles or San Francisco Bay Area) and contact: California Emergency Physicians, 440 Grand Ave., Suite 500, Oakland, CA 94610; (415) 832-6400.

OCCUPATIONAL MEDICINE STAFF POSITION available in well known Gulf South Multispecialty Clinic. Established full service occupational medicine program undergoing expansion. Excellent support from outstanding medical staff. Possible university appointment. Must be Board eligible/certified in Occupational Medicine with formal training in Occupational or Preventative Medicine. Excellent fringe benefits, salary negotiable. Send reply and CV to Box 6478, Western Journal of Medicine, 44 Gough St., San Francisco, CA 94103.

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GENERAL SURGEON OR FAMILY PRACTITIONER with general survery credentials wanted for a rural Washington State community. Full service hospital with drawing area of 6,000. Office space and ancillary services offered. Good opportunity in an agricultural four-season recreational area. Contact: Garvin Olson, Administrator, Janice Davis, Secretary, 1012 South Third, Dayton, WA 99328; (509) 382-2531.

PHYSICIAN WANTED: San Francisco B/C or B/E Internist/FP to join growing three man primary care group in San Francisco's Mission District. For further information contact Dr John Pierce, (415) 826-7575 or send résumé to Golden Gate Medical Group, 3620 Army St., San Francisco, CA 94110.

WANTED: American trained BC/BE Family Physician to join BC practitioner in pretty New Mexico town on the Pecos River. All outdoor activities available. Full benefits/salary negotiable. Reply: Box 6480, The Western Journal of Medicine, 44 Gough St., San Francisco, CA 94103.

INFECTIOUS DISEASE AND INTERNAL MEDICINE—The Division of General Internal Medicine/Primary Care at Cook County Hospital wishes to recruit an Attending Physician to supervise care of both patients with general medical problems and patients with AIDS. Board eligibility in Internal Medicine is required; subspecialty training in Infectious Disease or Oncology is desirable. General Medicine responsibilities occupy 50 percent time and include ward attending and supervising the General Medicine Clinic. AIDS service responsibilities include participation in biweekly clinics and regular ward consultations for patients with AIDS and AIDS related conditions, and involvement in educational and research programs of the AIDS service. Sensitivity to the health care needs of gay men and other AIDS risk group members is needed. Starting salary for Board certified physicians is $54,228 a year. For further information please contact Renslow Sherer, MD, Coordinator of AIDS Services, Division of General Medicine, Cook County Hospital, 1835 W. Harrison, Chicago, IL 60612. Cook County Hospital is an Equal Opportunity/Affirmative Action Employer.

PRIMARY CARE/URGENT CARE

Primary Care—Northern and Southern California: Part- or full-time positions for Primary Care physicians experienced in treatment of industrial type trauma for Occupational Health Clinics. Fringe benefits, malpractice insurance provided.

Urgent Care—Northern and Southern California: Rapidly expanding medical group servicing Urgent Care network throughout California (San Diego, Orange County, San Joaquin Valley and Bay areas) needs independent contractors with primary care, ER, occupational medicine specialties. California license required, prior out-patient practice a plus. Client provides all personnel, facility, ancillary equipment with group providing malpractice. Guaranteed minimum plus monthly incentive, stock options available. No relocation assistance. Write: Personnel, Urgent Care Centers of America, Inc. 2737 Walsh Ave., Santa Clara, CA 95051; (408) 727-1900; EOE.

INTERNIST-RHEUMATOLOGIST-SUBSPECIALIST. Opportunity to join solo Internist-Rheumatologist in private practice. Assocation and investment opportunity. Laboratory and x-ray. Send CV to R. S. Gordon, MD, 5945 Brockton Ave., Riverside, CA 92506.

CHILD OR ADOLESCENT PSYCHIATRIST: Immediate opening available to join well-established private practice group. Long-standing referral sources ensure full outpatient practice. Affiliated with three psychiatric inpatient units and University psychiatric residency program. Contact: James A. Margolis, MD, or J. Allen Miller, MD, Sacramento Child Guidance Center Medical Group, Inc., 3449 Mission Ave., Carmichael, CA 95608; (916) 481-3971.

PHYSICIANS WANTED

WASHINGTON—Ambulatory Care Center, Tacoma. Full- or possibly part-time for FP/IM/EM trained physician. Contact Roger Simms, MD, (206) 759-6655 or reply with CV to 5702 North 26th, Tacoma, WA 98407.

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(209) 297-7748

RHEUMATOLOGIST needed to join 38-member multispecialty group located on Central Coast of California. Board certified or eligible; California license. Excellent practice opportunity, benefits and retirement program, all practice costs paid, early shareholder status. Reply: David E. Graham, Assistant Administrator, San Luis Medical Clinic, Ltd., 1235 Osos St., San Luis Obispo, CA 93401.

HEMATOLOGIST-ONCOLOGIST to join Oncologist in progressive multispecialty group practice located in suburban San Francisco area. University affiliation and NCOG protocol participation encouraged. Competitive salary and benefits leading to partnership. Send résumé to Box 6479, The Western Journal of Medicine, 44 Gough St., San Francisco, CA 94103.

FAMILY PRACTICE-INTERNAL MEDICINE-SURGEON. Multispecialty clinic in Northern Idaho Panhandle. Nominal lease includes fully-equipped office and treatment suites with receptionist and janitorial services provided. Clinic includes lab, x-ray and pharmacy. Billing services available. Located in a four-season playground rich with forests, lakes, streams and wild game. Just 20 minutes from a 14-run ski resort. Attractive lifestyle. For information: (208) 784-1221, ext. 304. Mail résumé to: Shoshone Medical Center, Jacobs Gulch, Kellogg, ID 83837.

PHYSICIAN, FAMILY PRACTICE OR GENERAL PRACTICE needed for an exciting position with an innovative primary health care system. Skiing and camping nearby. Excellent salary, fringe benefits and continuing educational opportunities. Write to Jim Riebsomer, Farmington Community Health Center, PO Box 3239, Farmington, NM 87599.

SITUATIONS WANTED

EXPERIENCED Board certified Internist seeks two person association, or small group practice within or close to San Francisco. Spanish spoken. Interested in Occupational Medicine and Disability Evaluations. Please respond to Box 6474, Western Journal of Medicine, 44 Gough St., San Francisco, CA 94103.

PRIMARY CARE PHYSICIAN licenced in State of Washington seeks a position as house officer in a hospital/clinic and interested in buying a small practice or partnership in a group family practice in Washington. Write to Dr G. Pillai, 7753 Ontario St., Vancouver, BC, Canada V5X 3C6; (604) 324-3609.

NUTRITION/BARIATRICS—UNIQUE PHYSICIAN desires unique/innovative position in nutrition, bariatrics, health-promotion. Currently university-based academic internist. University-trained, ABIM-certified, member-ACP. Expertise in microcomputers. Creative. Problem-solving. Professional/entertaining approach: can give/take direction. Skilled in public presentations. Southwest locale necessary. Confidential reply to Journal Response, 270 North Canon Dr., Suite 103-Box 1020, Beverly Hills, CA 90210.

(Continued on Page 888)

AIDS: A WORLDWIDE EPIDEMIC

The San Francisco Medical Society and the Bay Area Physicians for Human Rights are co-sponsoring a one-day tutorial and discussion conference on AIDS with national experts in the field, with special emphasis on spread to the heterosexual community.

Saturday, June 29, 1985

San Francisco Medical Society Auditorium
250 Masonic Avenue, San Francisco, California

Subjects to be covered include:

AIDS virus(es) and transmission
Worldwide epidemiology
San Francisco epidemiologic studies
Management of opportunistic infections
Public health and societal impact
Transfusion AIDS
Antibody testing
Management of malignancies
AIDS-related conditions
AIDS research programs and funding
Chemotherapeutic agents

Registration Fee: $85.00 ($95.00 after June 15)
$50.00 for medical students with proof of status

Registration includes Lunch and a Wine and Cheese Reception at 5:30 PM

BAPHR Bay Area Physicians for Human Rights

FOR MORE INFORMATION
Call the SFMS (Steve Heilig)
at (415) 567-6230
or the Bay Area Physicians
for Human Rights
at (415) 558-9353

SFMS San Francisco Medical Society

CONTINUING MEDICAL EDUCATION

(Continued from Page 878)

June 26-28—**Community Support Systems for the Chronically Mentally Ill.** Seattle. Wednesday-Friday. Contact: U/W.

June 26-29—**(OREGON) Washington State Chapter, American College of Surgeons.** Sun River, Oregon. Wednesday-Saturday. Sun River Resort. Contact: Richard P. Billingham, MD, 801 Broadway, Suite 712, Seattle 98122. (206) 624-2107.

June 28—**Riverton Hospital Lectures.** Seattle. Friday. Riverton Hospital. Contact: U/W.

June 29-July 3 (CALIFORNIA)—**Pacific Coast Oto-Ophthalmological Society Annual Meeting.** San Diego. Saturday-Wednesday. Hotel Del Coronado. Contact: Robert E. Christensen, MD, Exec. Secretary-Treasurer, JSEI-UCLA, 800 Westwood Plaza, Los Angeles, CA 90024. (213) 625-5298.

July 8-10—**Scientific Aspects of Dance/Exercising Women.** Seattle. Monday-Wednesday. Sheraton. Contact: U/W.

July 8-12—**Sleep Disorders 1985.** Seattle. Monday-Friday. Westin. Contact: U/W.

August 2-4—**Washington State Society of Anesthesiologists Seafair VII Meeting—Anesthesia Care for Trauma.** Seattle. Friday-Sunday. Seattle Sheraton Hotel. Contact: Patti Smith, Washington State Society of Anesthesiologists, 2033 Sixth Ave., Ste. 900, Seattle 98121. (206) 441-9762.

August 2-5—**Refractive Surgery—State of the Art.** Orcas Island. Friday-Monday. Rosario Resort. Contact: Patti Smith, Washington State Academy of Ophthalmology, 2033 Sixth Ave., Ste. 900, Seattle 98121. (206) 441-9762.

September 6-7—**Washington State Society of Anesthesiologists Fall Meeting.** Hood Canal. Friday-Saturday. Alderbrook Inn. Contact: Patti Smith, Washington State Society of Anesthesiologists, 2033 Sixth Ave., Ste. 900, Seattle 98121. (206) 441-9762.

September 19-22—**Washington State Medical Association Annual Meeting.** Jantzen Beach. Thursday-Sunday. Thunderbird Motor Inn. Contact: Patti Smith, WSMA, 2033 Sixth Ave., Ste. 900, Seattle 98121. (206) 441-9762.

(Continued on Page 889)

(Continued from Page 886)

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SANTA CRUZ, CALIFORNIA. New office 1,377 square feet for rent or sale. Office lots for sale next to area's busiest hospital. R. E. Finegan, MD, (408) 475-8700.

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NORTH IDAHO—Excellent summer/winter recreational area. College community. Coeur d'Alene professional medical center has 1,512 square feet attractive, fully-equipped office for sub-lease with option to buy. Available August 1, 1985. Independent lab and x-ray department in building. Next door to well-equipped hospital. Send correspondence to Ironwood Medical Center, 920 Ironwood Dr., Coeur d'Alene, ID 83814 or phone Ann Poole at (208) 664-9139 or (208) 773-9495.

PRACTICES AVAILABLE

DEVELOPING HOSPITAL-BASED FAMILY PRACTICE in semi-rural coastal town 25 miles south of San Francisco. Easy access to the entire Bay Area. Contact: Dr Timothy Whelan, St. Catherine Hospital, Moss Beach, CA 94038; (415) 728-3366.

SACRAMENTO OPPORTUNITY. Established and growing Family Practice. 1984 gross, $260,000. Call or write Professional Practice Services at 884 Lincoln Way, Suite 38, Auburn, CA 95602. W. Pierce, Agent; (916) 823-2340.

OPHTHALMOLOGY PRACTICE FOR SALE: 1985 or 1986. Pacfic Northwest Coast. Office building for lease or sale. Retiring. Will stay to introduce. Reply including CV to Box 6472, Western Journal of Medicine, 44 Gough St., San Francisco, CA 94103.

INTERNAL MEDICINE—LA JOLLA, CALIFORNIA. Long established solo practice, retiring well equipped, recently redecorated office, will introduce, reply Box 6476, Western Journal of Medicine, 44 Gough St., San Francisco, CA 94103.

PEDIATRIC AND ALLERGY PRACTICE located in the Sierra Foothills for sale. Stable 13-year practice including all equipment, located in Medical/Dental Center featuring laboratory and x-ray facilities. Expanding 100+ bed Community Hospital located close to office. Send inquiries to: Administrator, PO Box 1961, Stockton, CA 95202.

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ONLINE LITERATURE SEARCHES—SHARES medical library services can deliver the best in bibliographic literature retrieval services to your home or office computer! Write to Library Services, Sacred Heart General Hospital, PO Box 10905, Eugene, OR 97440; or call (503) 686-6837, or 1 (800) 452-2639 in Oregon. MEDMAIL-MCSSHEARTGE.

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Mail to **DIVERS ALERT NETWORK**, Box 3823, Duke University Medical Center, Durham, N.C. 27710

CONTINUING MEDICAL EDUCATION

(Continued from Page 887)

September 28-October 4 (SAN JUAN ISLANDS)—**Effective Management of Common Sports Injuries.** Saturday-Friday. Contact: Epic Medical Expeditions, PO Box 209, Sun Valley, ID 83353. (206) 788-4995.

November 1-2 (VANCOUVER)—**Northwest Urological Society 1985 Annual Meeting.** Vancouver, BC. Friday-Saturday. Bayshore Inn. Contact: Patti Smith, Northwest Urological Society, 2033 Sixth Ave., Ste. 900, Seattle 98121. (206) 441-9762.

November 7-8—**Washington Chapter, American College of Emergency Physicians—15th Annual Clinic Conference.** Seattle. Thursday-Friday. Four Seasons Olympic Hotel. Contact: Patti Smith, Washington Chapter, ACEP, 2033 Sixth Ave., Suite 900, Seattle 98121. (206) 441-9762.

December 7-8—**Washington State Society of Anesthesiologists Winter Meeting.** Seattle. Saturday-Sunday. Four Seasons Olympic Hotel. Contact: Patti Smith, Washington State Society of Anesthesiologists, 2033 Sixth Ave., Suite 900, Seattle 98121. (206) 441-9762.

WYOMING

June 23-26—**Wyoming Medical Society—Annual Meeting.** Jackson Lake Lodge, Moran. Sunday-Wednesday. Contact: WMS, PO Drawer 4009, Cheyenne 82003-4009.

August 26-28—**Tutorials in the Tetons: Clinical Cardiology, Diagnostic and Therapeutic Advances.** Jackson Lake Lodge, Grand Teton National Park, Moran. Monday-Wednesday. Sponsor: American College of Cardiology. Contact: ACC, Extramural Prog. Dept., 9111 Old Georgetown Rd., Bethesda, MD 20814. (301) 897-5400, ext. 230.

September 7-12—**Applications in Preventive Medicine.** Yellowstone National Park Bicycle Tour. Saturday-Friday. 24 hrs. Cat. I. Sponsors: University of Arizona College of Medicine and Epic Medical Expeditions. Contact: Richard Paris, MD, PO Box 209, Sun Valley, ID 83353. (208) 788-4995. ◆

WESTERN STATE MEDICAL ASSOCIATIONS' MEETINGS

Alaska State Medical Association—4107 Laurel St., Anchorage 99504. (907) 562-2662. Annual Meeting: June 5-8, 1985, Haines.

Arizona Medical Association, Inc.—810 W. Bethany Home Rd., Phoenix 85013. (602) 246-8901. Annual Meeting: 1986: date and place to be announced.

California Medical Association—44 Gough St., San Francisco 94103. (415) 863-5522. Annual Meeting: February 28-March 5, 1986, Bonaventure Hotel, Los Angeles.

Colorado Medical Society—6825 E. Tennessee, Bldg. 2, Suite 500, Denver 80224. (303) 321-8590. Annual Meeting: September 11-14, 1985, Broadmoor, Colorado Springs.

Hawaii Medical Association—320 Ward Ave., Suite 200, Honolulu 96814. (808) 536-7702. Annual Meeting: October 12-14, 1985, Kona Surf Hotel, Kona.

Idaho Medical Association—305 W. Jefferson, PO Box 2668, Boise 83701. (208) 344-7888. Annual Meeting: July 24-27, 1985, Sun Valley.

Montana Medical Association—2012 11th Ave., Suite 12, Helena 59601. (406) 443-4000. Annual Meeting: October 3-5, 1985, Outlaw Inn, Kalispell.

Nevada State Medical Association—3660 Baker Lane, Reno 89502. (702) 825-6788. Annual Meeting: 1986: date and place to be announced.

New Mexico Medical Society—303 San Mateo NE, Suite 204, Albuquerque 87108. (505) 266-7868. Annual Meeting: 1986: date and place to be announced.

Oregon Medical Association—5210 S.W. Corbett Ave., Portland 97201. (503) 226-1555. Annual Meeting: (House of Delegates only): 1986: date and place to be announced.

Utah State Medical Association—540 East Fifth South, Salt Lake City 84102. (801) 355-7477. Annual Meeting: September 26-27, 1985. Hotel Utah, Salt Lake City.

Washington State Medical Association—900 United Airlines Bldg., 2033 6th Ave., Seattle 98121. (206) 623-4801. Annual Meeting: September 19-22, 1985, Jantzen Beach.

Wyoming Medical Society—P.O. Drawer 4009, Cheyenne 82003-4009. (307) 635-2424. Annual Meeting: June 23-26, 1985, Jackson Lake Lodge, Moran.

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Before prescribing, please consult complete product information, a summary of which follows:

Indications: Relief of moderate to severe depression associated with moderate to severe anxiety

Contraindications: Known hypersensitivity to benzodiazepines or tricyclic antidepressants. Do not use with monoamine oxidase (MAO) inhibitors or within 14 days following discontinuation of MAO inhibitors since hyperpyretic crises, severe convulsions and deaths have occurred with concomitant use, then initiate cautiously, gradually increasing dosage until optimal response is achieved. Contraindicated during acute recovery phase following myocardial infarction.

Warnings: Use with great care in patients with history of urinary retention or angle-closure glaucoma. Severe constipation may occur in patients taking tricyclic antidepressants and anticholinergic-type drugs. Closely supervise cardiovascular patients (Arrhythmias, sinus tachycardia and prolongation of conduction time reported with use of tricyclic antidepressants, especially high doses. Myocardial infarction and stroke reported with use of this class of drugs.) Caution patients about possible combined effects with alcohol and other CNS depressants and against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving).

***Usage in Pregnancy*: Use of minor tranquilizers during the first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**

Since physical and psychological dependence to chlordiazepoxide have been reported rarely, use caution in administering Limbitrol to addiction-prone individuals or those who might increase dosage; withdrawal symptoms following discontinuation of either component alone have been reported (nausea, headache and malaise for amitriptyline; symptoms [including convulsions] similar to those of barbiturate withdrawal for chlordiazepoxide).

Precautions: Use with caution in patients with a history of seizures, in hyperthyroid patients or those on thyroid medication, and in patients with impaired renal or hepatic function. Because of the possibility of suicide in depressed patients, do not permit easy access to large quantities in these patients. Periodic liver function tests and blood counts are recommended during prolonged treatment. Amitriptyline component may block action of guanethidine or similar antihypertensives. Concomitant use with other psychotropic drugs has not been evaluated, sedative effects may be additive. Discontinue several days before surgery. Limit concomitant administration of ECT to essential treatment. See Warnings for precautions about pregnancy. Limbitrol should not be taken during the nursing period. Not recommended in children under 12. In the elderly and debilitated, limit to smallest effective dosage to preclude ataxia, oversedation, confusion or anticholinergic effects.

Adverse Reactions: Most frequently reported are those associated with either component alone: drowsiness, dry mouth, constipation, blurred vision, dizziness and bloating. Less frequently occurring reactions include vivid dreams, impotence, tremor, confusion and nasal congestion. Many depressive symptoms including anorexia, fatigue, weakness, restlessness and lethargy have been reported as side effects of both Limbitrol and amitriptyline. Granulocytopenia, jaundice and hepatic dysfunction have been observed rarely.

The following list includes adverse reactions not reported with Limbitrol but requiring consideration because they have been reported with one or both components or closely related drugs:

Cardiovascular: Hypotension, hypertension, tachycardia, palpitations, myocardial infarction, arrhythmias, heart block, stroke.

Psychiatric: Euphoria, apprehension, poor concentration, delusions, hallucinations, hypomania and increased or decreased libido.

Neurologic: Incoordination, ataxia, numbness, tingling and paresthesias of the extremities, extrapyramidal symptoms, syncope, changes in EEG patterns.

Anticholinergic: Disturbance of accommodation, paralytic ileus, urinary retention, dilatation of urinary tract.

Allergic: Skin rash, urticaria, photosensitization, edema of face and tongue, pruritus.

Hematologic: Bone marrow depression including agranulocytosis, eosinophilia, purpura, thrombocytopenia.

Gastrointestinal: Nausea, epigastric distress, vomiting, anorexia, stomatitis, peculiar taste, diarrhea, black tongue.

Endocrine: Testicular swelling and gynecomastia in the male, breast enlargement, galactorrhea and minor menstrual irregularities in the female, elevation and lowering of blood sugar levels, and syndrome of inappropriate ADH (antidiuretic hormone) secretion.

Other: Headache, weight gain or loss, increased perspiration, urinary frequency, mydriasis, jaundice, alopecia, parotid swelling.

Overdosage: Immediately hospitalize patient suspected of having taken an overdose. Treatment is symptomatic and supportive. I.V. administration of 1 to 3 mg physostigmine salicylate has been reported to reverse the symptoms of amitriptyline poisoning. See complete product information for manifestation and treatment.

Dosage: Individualize according to symptom severity and patient response. Reduce to smallest effective dosage when satisfactory response is obtained. Larger portion at daily dose may be taken at bedtime. Single *h.s.* dose may suffice for some patients. Lower dosages are recommended for the elderly.

Limbitrol DS (double strength) Tablets, initial dosage of three or four tablets daily in divided doses, increased to six tablets or decreased to two tablets daily as required. Limbitrol Tablets, initial dosage of three or four tablets daily in divided doses, for patients who do not tolerate higher doses.

How Supplied: *Double strength (DS) Tablets*, white, film-coated, each containing 10 mg chlordiazepoxide and 25 mg amitriptyline (as the hydrochloride salt), and *Tablets*, blue, film-coated, each containing 5 mg chlordiazepoxide and 12.5 mg amitriptyline (as the hydrochloride salt)—bottles of 100 and 500; Tel-E-Dose® packages of 100, Prescription Paks of 50.

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